CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients

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Background: Venous thromboembolism (VTE) is a common source of perioperative morbidity and mortality.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support decision making about preventing VTE in patients undergoing surgery.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including performing systematic reviews. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 30 recommendations, including for major surgery in general (n = 8), orthopedic surgery (n = 7), major general surgery (n = 3), major neurosurgical procedures (n = 2), urological surgery (n = 4), cardiac surgery and major vascular surgery (n = 2), major trauma (n = 2), and major gynecological surgery (n = 2).

Conclusions: For patients undergoing major surgery in general, the panel made conditional recommendations for mechanical prophylaxis over no prophylaxis, for pneumatic compression prophylaxis over graduated compression stockings, and against inferior vena cava filters. In patients undergoing total hip or total knee arthroplasty, conditional recommendations included using either aspirin or anticoagulants, as well as for a direct oral anticoagulant over low-molecular-weight heparin (LMWH). For major general surgery, the panel suggested pharmacological prophylaxis over no prophylaxis, using LMWH or unfractionated heparin. For major neurosurgery, transurethral resection of the prostate, or radical prostatectomy, the panel suggested against pharmacological prophylaxis. For major trauma surgery or major gynecological surgery, the panel suggested pharmacological prophylaxis over no prophylaxis.

Summary of recommendations

These American Society of Hematology (ASH) guidelines are based on updated and original systematic reviews of evidence conducted by researchers and developed under the direction of the McMaster

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University GRADE Centre with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine (now the National Academy of Medicine) and the Guidelines International Network.[1-4] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[5,6] to assess the certainty in the evidence and formulate recommendations.

The population of postoperative patients is heterogeneous with regard to the degree of risk of venous thromboembolism (VTE), depending on intrinsic patient factors and those factors that are related to the type of surgery, mobilization, anatomic location of the procedures, and risk of bleeding. Surgeons have a long history of accepting prophylactic measures against VTE, be they mechanical or pharmacological.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient to arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Recommendations

Mechanical vs pharmacological prophylaxis for patients undergoing major surgery

RECOMMENDATIONS 1 TO 5. For patients undergoing major surgery, the ASH guideline panel *suggests* the following:

1. Using pharmacological prophylaxis or mechanical prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯)
2. For patients who do not receive pharmacologic prophylaxis, using mechanical prophylaxis over no mechanical prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
3. For patients who receive mechanical prophylaxis, using intermittent compression devices over graduated compression stockings (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
4. For patients who receive pharmacologic prophylaxis, using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
5. Depending on the risk of VTE and bleeding based on the individual patient and the type of surgical procedure, using combined prophylaxis or mechanical prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks: For patients considered at high risk of bleeding, the balance of effects may favor mechanical methods over pharmacological prophylaxis. For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Prophylactic insertion of an inferior vena cava filter

RECOMMENDATION 6. For patients undergoing major surgery, the ASH guideline panel *suggests against* using inferior vena cava (IVC) filters for prophylaxis of VTE (conditional recommendation based on very low certainty in the evidence of effects, ⊕◯◯◯).

Timing of antithrombotic prophylaxis

RECOMMENDATIONS 7 AND 8. For patients undergoing major surgery, the ASH guideline panel *suggests* using extended antithrombotic prophylaxis over short-term antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). The ASH guideline panel further *suggests* using early or delayed antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks**: Extended prophylaxis was generally considered as beyond 3 weeks (range, 19-42 days) compared with short-term prophylaxis, which was considered as up to 2 weeks (range, 4-14 days). Twelve hours following surgery was arbitrarily

selected to be the cutoff point between early and late postoperative antithrombotic administration.

Orthopedic surgery

RECOMMENDATIONS 9 TO 13. For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using aspirin (ASA) or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). When anticoagulants are used, the panel *suggests* using direct oral anticoagulants (DOACs) over low-molecular-weight heparin (LMWH) (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯); the panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). If a DOAC is not used, the panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) and *recommends* LMWH rather than unfractionated heparin (UFH) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

RECOMMENDATIONS 14 AND 15. For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Major general surgery

RECOMMENDATIONS 16 AND 17. For patients undergoing major general surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Laparoscopic cholecystectomy

RECOMMENDATION 18. For patients undergoing laparoscopic cholecystectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients with other risk factors for VTE (such as history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Major neurosurgical procedures

RECOMMENDATIONS 19 AND 20. For patients undergoing major neurosurgical procedures, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). For the subset of patients undergoing major neurosurgical procedures for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Patients undergoing major neurosurgical procedures are expected to receive prophylaxis with mechanical methods. Pharmacological prophylaxis may be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, pharmacological prophylaxis could be considered for patients undergoing major neurosurgical procedures that carried a lower risk for major bleeding and in those patients with persistent mobility restrictions after the bleeding risk declines following surgery.

Urological procedures

RECOMMENDATIONS 21 AND 22. For patients undergoing transurethral resection of the prostate (TURP), the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). For the subset of patients undergoing TURP for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients with other risk factors for VTE (such as history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

RECOMMENDATIONS 23 AND 24. For patients undergoing radical prostatectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). For patients undergoing radical prostatectomy in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis.

Cardiac or major vascular surgery

RECOMMENDATIONS 25 AND 26. For patients undergoing cardiac or major vascular surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis or no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). When pharmacological prophylaxis is used, the panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Major trauma

RECOMMENDATION 27A. For patients experiencing major trauma and who are at low to moderate risk for bleeding, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 27B. For patients experiencing major trauma and who are at high risk for bleeding, the ASH guideline panel *suggests against* pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 28. For patients experiencing major trauma in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Major gynecological surgery

RECOMMENDATIONS 29 AND 30. For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis

(conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about the prevention of VTE for patients undergoing major surgical procedures. The target audience includes patients, surgeons, intensivists, internists, hematologists, general practitioners, hospitalists, other clinicians, pharmacists, and decision makers. Policy makers interested in these guidelines include those involved in developing local, national, or international programs aiming to safely reduce the incidence of VTE and/or to evaluate direct and indirect harms and costs related to VTE and its prevention. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

Deep vein thrombosis (DVT) and pulmonary embolism (PE) (collectively, VTE) are well-recognized, clinically important, and potentially devastating complications that may occur following major surgical procedures, defined as any surgical intervention that carries greater than minimal risk, is performed in the operating room, and requires specialized training. Before the era of the routine use of effective prophylaxis, VTE was a common cause of morbidity and mortality following major surgery. It has been estimated to cause >50 000 deaths per annum in the United States alone.[7] The importance of preventative measures to minimize the risk of VTE following major surgery has been recognized for decades; however, even with the use of prophylaxis, surgery accounts for ~25% of VTEs observed in communities.[8]

Although most surgical procedures carry some risk for VTE, this risk varies considerably across surgical procures and among individual patients undergoing surgery. Surgical procedures carrying the highest risk of developing postoperative VTE include hip and knee arthroplasty, invasive neurosurgical procures, and major vascular procedures.[9]

Patient factors that carry greater risks for thrombosis include histories of VTE, particularly if unprovoked or associated with cancer, or cancer, even in the absence of previous VTE. Scoring systems that calculate the risk of postoperative VTE for individual patients, such as the Caprini score, have been developed and validated following some surgical procedures.[10]

Although postoperative VTE has historically been a complication primarily occurring in the hospital, with shortened hospital stays, postoperative VTE often occurs in the days to weeks following discharge from the hospital.[11]

Description of the target populations

The primary target population of this guideline is patients hospitalized for major surgical procedures that carry a risk for postoperative VTE. This guideline also addresses patients hospitalized following major trauma; most, but not all, subsequently required major surgical procedures. The panel recognized that there are 2 major modalities applied for the prevention of VTE in the postoperative period: pharmacological antithrombotic prophylaxis and mechanical prophylaxis. For evaluation of the pharmacological methods for the prevention of VTE, the panel weighed the benefits and risks of the various options for individual surgical procedures or domains, such as hip or knee arthroplasty, general surgery, or urological or neurosurgical procedures.

For mechanical interventions, such as graduated or mechanical compression devices or IVC filters, the effectiveness of these interventions was assessed across all surgical domains. Likewise, other questions, such as the duration of pharmacological prophylaxis and timing of the initiation of pharmacological prophylaxis, were also assessed across all surgical domains.

The target populations included patients who underwent surgery for cancer or noncancer-related procedures. Patients hospitalized for major trauma were included whether they underwent surgery or not.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[5,6,12-16] The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guidelines International Network–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[1-4]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 9 other guideline panels (addressing other aspects of VTE management) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (Adam Cuker) and vice chair (H.J.S.). ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process, including the use of the GRADE approach. The membership of the panels and the GRADE Centre team is described in Supplement 1.

The panel included surgeons with subspecialty representation, hematologists, internists, and a pharmacist, all of whom had clinical and research expertise on the guideline topic. The panel also included methodologists with expertise in evidence appraisal and guideline development and 2 patient representatives. Both patient representatives participated in question prioritization, and 1 participated in all remaining steps of the development process. The panel chair was a content expert. The vice chair was a urological surgeon with specialized expertise in guideline development.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline-development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (www.surveymonkey.com and www.gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Some members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. The patient representative (C.B.) received an honorarium of $200. The panelists received no other payments. Some researchers who contributed to the systematic evidence reviews received salary or grant support through the McMaster GRADE Centre. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine[17] and the Guidelines International Network.[4] At the time of appointment, a majority of the guideline panel, including the chair and the vice chair, had no conflicts of interest as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but the majority continued to have no conflicts of interest with commercial entities, as judged by ASH.

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms of all panel members. In Part A of the forms, individuals disclosed material interests for 2 years prior to appointment. In Part B, they disclosed other interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was used to manage conflicts of interest. During deliberations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines participated in discussions about the evidence and clinical context but were recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) and the direction and strength of relevant recommendations.[4,18-20] The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

None of the McMaster-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current material interest in a commercial entity with any product that could be affected by the guidelines. Supplement 3 provides the complete "Disclosure of Interest" forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradepro.org) and SurveyMonkey (www.surveymonkey.com) to brainstorm and then prioritize the questions described in Table 1.

The panel selected outcomes of interest for each question a priori, following an approach described in detail elsewhere.[21] The panel rated the following outcomes as critical for clinical decision making across all questions: mortality, symptomatic PEs, symptomatic proximal DVTs, symptomatic severe distal DVTs, major bleeding, and reoperation. The panel used an explicit process to rate the clinical severity of DVTs and PEs. The panel determined that all symptomatic proximal DVTs and PEs confirmed by objective diagnostic imaging were considered of moderate severity and were clinically important.[22] For several outcomes, the studies reported outcomes that were different or were in addition to the outcomes that the panel determined to be important for decision making. Typically, included studies reported outcomes as any PE, any DVT, or any proximal or distal DVT. Some studies did not distinguish asymptomatic thromboembolic events that were detected by the routine performance of sensitive screening studies for VTEs from symptomatic thromboembolic events where patients developed overt symptoms that were subsequently confirmed by objective testing to be associated with VTEs. Reporting of symptomatic thromboembolic events was inconsistent across studies.

Where available, questions were addressed with studies that reported symptomatic outcome events. In the absence of reports of symptomatic VTE in a clinical question, modeling was performed using estimates of the proportion of asymptomatic DVTs that would become clinically important symptomatic events (Supplement 4). Only "severe" distal DVTs were rated as clinically important distal DVTs, and it was estimated that only ~25% of symptomatic postoperative distal DVTs would be considered severe.

Major bleeding definitions varied across clinical studies. For the purposes of this analysis, outcome events that met the definition of major bleeding for individual studies were applied. The exception was that the need for a blood transfusion itself was not considered major bleeding unless other criteria for major bleeding were met. The definition of reoperation was not specific for reoperation caused by or related to major bleeding.

Studies evaluated included patients with cancer and without cancer. We tested potential differences in the effects on studies with >50% and <50% of participants with cancer. Subgroup analyses did not demonstrate a difference in the relative effectiveness of interventions whether cancer patients were included or not. As a result, recommendations do not distinguish between cancer and noncancer patients.

For the use of pharmacological and mechanical methods of prophylaxis, the panel advises to follow manufacturer's recommendations regarding patient-specific restrictions in the use of individual products (such as levels of renal function for patients receiving LMWHs or DOACs). The panel also advises periodic monitoring of the platelet count for patients receiving LMWH and, in particular, UFH, as postoperative prophylaxis in consideration of the risk of heparin-induced thrombocytopenia.

Table 1. Prioritized clinical questions

Perioperative VTE prophylaxis in major surgery in general
1. Pharmacological prophylaxis vs mechanical prophylaxis
2. Mechanical prophylaxis vs no prophylaxis
3. Pneumatic compression devices vs graduated compression stockings
4. Pharmacological prophylaxis combined with mechanical prophylaxis vs pharmacological prophylaxis alone
5. Mechanical prophylaxis combined with pharmacological prophylaxis vs mechanical prophylaxis alone
6. Insertion of an IVC filter vs no IVC filter
7. Extended antithrombotic prophylaxis vs short-term antithrombotic prophylaxis
8. Early vs delayed antithrombotic prophylaxis
Orthopedic surgery: total hip and knee arthroplasty
9. ASA prophylaxis vs anticoagulants
10. DOAC prophylaxis vs LMWH prophylaxis
11. DOAC prophylaxis vs prophylaxis with another DOAC
12. LMWH prophylaxis vs warfarin prophylaxis
13. LMWH prophylaxis vs UFH prophylaxis
Orthopedic surgery: hip fracture repair
14. Pharmacological prophylaxis vs no pharmacological prophylaxis
15. LMWH prophylaxis vs UFH prophylaxis
Major general surgery
16. Pharmacological prophylaxis vs no pharmacological prophylaxis
17. LMWH prophylaxis vs UFH prophylaxis
Laparoscopic cholecystectomy
18. Pharmacological prophylaxis vs no pharmacological prophylaxis
Major neurosurgical procedures
19. Pharmacological prophylaxis vs no pharmacological prophylaxis
20. LMWH prophylaxis vs UFH prophylaxis
TURP
21. Pharmacological prophylaxis vs no pharmacological prophylaxis
22. LMWH prophylaxis vs UFH prophylaxis
Radical prostatectomy
23. Pharmacological prophylaxis vs no pharmacological prophylaxis
24. LMWH prophylaxis vs UFH prophylaxis
Cardiac or major vascular surgery
25. Pharmacological prophylaxis vs no pharmacological prophylaxis
26. LMWH prophylaxis vs UFH prophylaxis
Major trauma
27. Pharmacological prophylaxis vs no pharmacological prophylaxis
28. LMWH prophylaxis vs UFH prophylaxis
Major gynecological surgery
29. Pharmacological prophylaxis vs no pharmacological prophylaxis
30. LMWH prophylaxis vs UFH prophylaxis

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[12,13,16] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (Supplement 5) were updated during October and November 2016, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions. Monthly search alerts were created and monitored to capture relevant new studies up to 1 July 2019, prior to submission of the manuscript for publication.

Under the direction of the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.[12,13,16] Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[5,6,14]

During a 2-day in-person meeting, followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. In the event that consensus was not reached based on discussion, the recommendation was made based on a vote of the panel, with the results of such votes listed in the text following the recommendation. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" is used for conditional recommendations.

Table 2. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Table 2 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and health care policy makers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 22 June 2018 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Sixteen individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to the recommendations. The guidelines were reviewed by the ASH Guideline Oversight Subcommittee on 28 August 2019, approved by the Committee on Quality on 6 September 2019 and by the ASH officers on 13 September 2019, and then subjected to peer review.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary-of-findings tables in each section.

Recommendations

Mechanical vs pharmacological prophylaxis for patients undergoing major surgery

Question: Should pharmacological prophylaxis vs mechanical prophylaxis be used for patients undergoing major surgery?

Recommendation 1

For patients undergoing major surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis or mechanical prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). **Remark:** For patients considered at high risk for bleeding, the balance of effects may favor mechanical methods over pharmacological prophylaxis.

Summary of the evidence. We identified 11 systematic reviews addressing, in part, this question.[23-33] We identified 38 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[34-72] Our systematic search of randomized controlled trials (RCTs) identified 2 additional studies not included in previous systematic reviews and that fulfilled the inclusion criteria.[70,72]

Fifteen studies reported the effect of the pharmacological prophylaxis compared with mechanical prophylaxis alone on risk of mortality.[35,36,40,42,51,54,57,59-61,63-65,68,72] Thirteen studies reported the effect on the development of symptomatic PEs,[35,37,39,43,45,62,64,67-72] and 17 studies reported the effect on the development on any PE.[34,36,38,40,42,46,47,50,51,53,58,60,61,63,67,71,72] Six studies reported data on symptomatic DVTs,[35,67,69-72] and 17 studies reported data on any proximal DVT.[34,35,37,39,41,45,52,53,57,58,64,65,67,69-72] Four studies reported data on symptomatic distal DVTs,[35,70-72] and 16 studies reported data on any distal DVT.[34,35,37,39,40,45,52,53,57,58,63,64,66,67,71,72]

Eighteen studies reported the effect of pharmacological prophylaxis compared with mechanical prophylaxis alone on the risk of major bleeding,[35-37,41,42,43,48,51,54,59-61,63-66,68,72] and 6 studies reported the effect on the risk of reoperation.[37,42,46,48,54,72]

The EtD framework is available at https://guidelines.gradepro.org/profile/B57A59FE-FCA9-8C9A-8C8D-55089B4E8FB1.

Benefits. The systematic review found that there may be no difference in mortality between pharmacological and mechanical prophylaxis (relative risk [RR], 0.92; 95% confidence interval [CI], 0.46-1.84; low certainty in the evidence of effects); this corresponds to 1 fewer (5 fewer to 7 more) death per 1000 patients. Similarly, irrespective of the baseline risk chosen, which was derived from a cohort study of 172 320 patients,[73] there may be no difference for symptomatic PEs (RR, 1.04; 95% CI, 0.36-2.96; low certainty in the evidence of effects), corresponding to 0 fewer events (2 fewer to 7 more). There is also likely little to no difference in symptomatic proximal DVTs (RR, 0.75; 95% CI, 0.11-5.32; moderate certainty in the evidence of effects); depending on the baseline risk of 1.6% or 2.6%,[73] this corresponds to anywhere from 4 fewer (15 fewer to 71 more) to 7 fewer (23 fewer to 113 more) events, respectively. For symptomatic distal DVTs, pharmacological prophylaxis likely results in a reduction in risk (RR, 0.16; 95% CI, 0.05-0.58; moderate certainty in the evidence of effects); however, this corresponds to a possibly small, and likely unimportant, reduction in symptomatic distal DVTs in absolute terms of 2 fewer (1-2 fewer) per 1000 patients, based on a baseline risk of 1.2% from observational data.[73]

Harms and burden. Pharmacological prophylaxis likely leads to more major bleeding (RR, 2.87; 95% CI, 1.68-4.92; moderate certainty in the evidence of effects). This corresponds to a small absolute increase of 12 more (4-25 more) major bleeds per 1000 patients. Pharmacological prophylaxis probably results in no difference in reoperations (RR, 2.01; 95% CI, 0.29-14.05; low certainty in the evidence of effects), corresponding to 1 more (1 fewer to 19 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading twice for very serious imprecision.

Other EtD criteria and considerations. The panel determined that, on balance, neither approach was favored over the other for patients undergoing major surgery at low or moderate risk for major bleeding because of the low certainty in the evidence, as well as concerns about compliance with mechanical prophylaxis. For patients at high baseline risk for major bleeding, mechanical prophylaxis would more clearly be favored because of the incremental risk of bleeding with pharmacological prophylaxis. There was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. The panel further judged the costs associated with pharmacological prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. Cost-effectiveness probably favors mechanical prophylaxis. The panel did not account for potential risks of mechanical prophylaxis, including fall risk, risk of skin damage, and limitation in mobility. There would probably be no impact on health equity, and pharmacological and mechanical prophylaxis would be acceptable to stakeholders and probably feasible to implement. The panel recognized that most of the evidence informing this recommendation came from the orthopedic literature (elective knee and hip arthroplasty).

Conclusions and research needs for this recommendation. The guideline panel suggests using pharmacological prophylaxis or mechanical prophylaxis for patients undergoing major surgery, based on low certainty in the evidence of effects. For patients deemed at high risk for major bleeding (because of the nature of the surgical procedure), there is likely a net benefit in favor of mechanical prophylaxis.

The panel determined that it would be valuable to have further high-quality studies comparing these interventions outside of the orthopedic setting to confirm the generalizability of the results across surgical domains. The panel would also welcome high-quality studies to determine the effectiveness of mechanical prophylaxis administered outside the hospital setting. The panel identified the need for more and better studies on how patients value the various outcomes in the perioperative setting and to what degrees these values vary by patients as a future research priority.

Question: Should mechanical prophylaxis vs no prophylaxis be used for patients undergoing major surgery?

Recommendation 2

For patients undergoing major surgery who do not receive pharmacologic prophylaxis, the ASH guideline panel *suggests* using mechanical prophylaxis over no mechanical prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 5 systematic reviews addressing, in part, this question.[24,25,27,28,30] We identified 25 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.[37,49,53,66,74-94] Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Ten studies reported the effect of mechanical prophylaxis compared with no prophylaxis on risk of mortality.[49,77,78,81,83-85,88,90,94] Nine studies reported the effect on the development of symptomatic PEs,[37,76,78,81,83,84,86,88,92] and 5 studies reported the effect on any PE.[53,77,85,86,93] No study reported data on symptomatic proximal or distal DVT, but 8 studies reported on any proximal DVT,[37,78,79,82,84,85,92,93] and 7 studies reported on any distal DVT.[37,77,79,82,85,92,93]

The EtD framework is available online at https://guidelines.gradepro.org/profile/61E7ADC1-4C91-8D58-9E3A-56BFEE3EAC20.

Benefits. There may be no difference in mortality between mechanical prophylaxis and no prophylaxis (RR, 1.33; 95% CI, 0.71-2.51; low certainty in the evidence of effects); this corresponds to 6 more (5 fewer to 28 more) deaths per 1000 patients. There may be a small difference in symptomatic PEs (RR, 0.61; 95% CI, 0.27-1.40; low certainty in the evidence of effects) corresponding to 3 fewer (6 fewer to 3 more) symptomatic PEs per 1000 patients based on a baseline risk of 0.8% and 4 fewer (8 fewer to 4 more) per 1000 patients based on a baseline risk of 1.1% from observational data.[73] There may be no difference in symptomatic proximal DVTs (RR, 0.75; 95% CI, 0.35-1.61; very low certainty in the evidence of effects), but we are uncertain of this. The risk of symptomatic distal DVTs may be

reduced (RR, 0.66; 95% CI, 0.50-0.86; very low certainty in the evidence of effects), but we are uncertain of this.

Harms and burden. There were no relevant adverse events deemed critical for this comparison. The panel was unable to assess the relative effect of mechanical prophylaxis on potential hazards, such as falls or skin complications.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, imprecision, and inconsistency.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors mechanical prophylaxis over no prophylaxis for patients at moderate or high risk for VTE but not patients at low risk for VTE. The panel judged the costs associated with mechanical prophylaxis to be moderate based on very low certainty in the evidence about resource requirements, with no available studies explicitly addressing this question. Cost-effectiveness probably favors mechanical prophylaxis. There would probably be no impact on health equity; mechanical prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel recognized that many patients considered at moderate to high risk for VTE would receive pharmacological prophylaxis in addition to mechanical methods. The guideline panel determined that there was very low certainty evidence for a net health benefit/harm for mechanical prophylaxis. Most of the evidence comes from orthopedics (elective hip and knee arthroplasty). In settings where intermittent pneumatic compression is not available, the use of stockings as mechanical prophylaxis is an acceptable and feasible option (see Recommendation 3).

Conclusions and research needs for this recommendation. For patients undergoing major surgery and at risk for VTE, the ASH guideline panel suggests using mechanical prophylaxis over no mechanical prophylaxis, recognizing that the certainty in the evidence is very low for this recommendation.

The panel recognizes that there is a need for high-quality clinical trials using clinically relevant end points to improve the certainty of the evidence supporting this recommendation, particularly outside the orthopedic setting. However, this is likely a lower priority for research than studies evaluating mechanical prophylaxis in combination with pharmacological prophylaxis.

Question: Should pneumatic compression devices vs graduated compression stockings be used for patients undergoing major surgery?

Recommendation 3

For patients undergoing major surgery who receive mechanical prophylaxis, the ASH guideline panel *suggests* using intermittent compression devices over graduated compression stockings (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 6 systematic reviews addressing this question.[25-28,31,32] We identified 11 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.[37,94-103] Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Five studies reported the effect of pneumatic compression prophylaxis compared with graduated compression stockings prophylaxis on risk of mortality.[94,96,97,101,102] Eight studies reported the effect on the development of symptomatic PEs,[37,95-99,102,103] and 4 studies reported the effect on any PE.[94,100,101,103] One study reported data on symptomatic proximal and symptomatic distal DVTs,[98] whereas 6 studies reported on any proximal DVT,[37,94,96,98-100] and 5 studies reported on any distal DVT.[37,94,96,98,100]

The EtD framework is available online at https://guidelines.grade-pro.org/profile/1584FD2F-9CC6-9C59-8DF5-48F0045F1BE5.

Benefits. There is no difference in mortality between pneumatic compression and graduated compression stockings prophylaxis (RR, 1.04; 95% CI, 0.16-6.63; low certainty in the evidence of effects); this corresponds to 2 more (41 fewer to 274 more) per 1000 patients. There may also be no difference in symptomatic PEs (RR, 0.56; 95% CI, 0.17-1.86; low certainty in the evidence of effects). The risk of symptomatic proximal DVTs may be reduced (RR, 0.48; 95% CI, 0.25-0.93, very low certainty in the evidence of effects), but we are uncertain of this finding. This benefit likely corresponds to 9 fewer (1-12 fewer) symptomatic proximal DVTs in 1000 patients with a baseline risk of 1.6% and 14 fewer (2-20 fewer) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 2.6% from observational data.[73] The risk of distal DVT (RR, 0.55; 95% CI, 0.25-1.22, very low certainty in the evidence of effects) appears to be similar, but we are uncertain of this finding.

Harms and burden. There were no relevant adverse events deemed critical for this comparison. Potential harms included reduced mobility, and pneumatic compression prophylaxis may be uncomfortable. There is also a small risk for inappropriate use of pneumatic compression prophylaxis for some patients (eg, those with lower extremity fractures).

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, imprecision, and inconsistency.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors pneumatic compression prophylaxis over graduated compression stockings prophylaxis. The panel was unable to assess the relative effect of pneumatic compression compared with that of graduated compression stockings on the risk of other hazards, such as falls or skin complications. These might be considered "unmeasured harms" of mechanical prophylaxis. The panel judged the costs associated with pneumatic compression prophylaxis to be moderate based on very low certainty in the evidence about resource requirements, with no available studies explicitly addressing this question. Cost-effectiveness probably favors pneumatic compression prophylaxis. There would probably be no impact on health equity; pneumatic compression prophylaxis would probably

be acceptable to stakeholders and probably feasible to implement. Lack of information regarding out-of-hospital use of pneumatic compression was a limitation of this technique. The panel recognizes that most of the evidence about the effectiveness comes from orthopedics (elective hip and knee arthroplasty).

Conclusions and research needs for this recommendation. The panel suggests using pneumatic compression devices over graduated compression stockings for patients undergoing major surgery, recognizing that there was very low certainty evidence for a net health benefit/harm. The recommendation applies to patients undergoing major surgery who are considered at risk for VTE.

In settings where pneumatic compression devices are not available, the use of graduated compression stockings is reasonable, because mechanical prophylaxis is an acceptable and feasible option. Further well-designed studies using clinically relevant end points are required to improve the quality of evidence related to this question. Studies outside the field of orthopedics would be particularly useful.

Question: Should combined pharmacological and mechanical prophylaxis vs pharmacological prophylaxis alone be used for patients undergoing major surgery?

Recommendation 4

For patients undergoing major surgery who receive pharmacologic prophylaxis, the ASH guideline panel *suggests* using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Summary of the evidence. We identified 7 systematic reviews addressing this question.[23-26,28,29,31-33] We identified 19 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.[36,60,62,68,70,104-117] Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Seven studies reported the effect of the combination of pharmacological and mechanical prophylaxis compared with pharmacological prophylaxis alone on the risk of mortality.[36,60,62,68,104,105,107] Ten studies reported the effect on the development of symptomatic PEs,[60,62,68,70,105,107,109-111,117] and 6 studies reported the effect on any PE.[36,104,108,112,116,117] Three studies reported data on symptomatic proximal DVTs,[62,70,112] and 8 studies reported data on any proximal DVT.[62,70,104,108,112-114] Three studies reported data on symptomatic distal DVTs,[70,105,112] and 7 studies reported on any distal DVT.[68,105,108,109,112-114] Six studies reported the effect of combination pharmacological and mechanical prophylaxis compared with pharmacological prophylaxis alone on the risk of major bleeding,[60,62,68,104,109,112] and 2 studies reported the effect on the risk of reoperation.[107,117]

The EtD framework is available online at https://guidelines.gradepro.org/profile/9AC669C6-30BB-C8DF-8430-3EDA0D4842C8.

Benefits. There may be no difference in mortality between pharmacological prophylaxis combined with mechanical prophylaxis and pharmacological prophylaxis alone (RR, 0.29; 95% CI, 0.06-1.38; low certainty in the evidence of effects); this corresponds to 5 fewer (7 fewer to 3 more) deaths per 1000 patients. There may be a reduction in symptomatic PEs (RR, 0.40; 95% CI, 0.25-0.65; low certainty in the evidence of effects) favoring combined prophylaxis. Depending on the baseline risk, this benefit likely corresponds to 5 fewer (3-6 fewer) per 1000 patients with a baseline risk of 0.8% to up to 7 fewer (4-8 fewer) per 1000 patients based on a baseline risk of 1.2% from observational data.[73] We are very uncertain whether the risks of symptomatic proximal DVTs (RR, 0.14; 95% CI, 0.01-2.63; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 1.99; 95% CI, 0.35-11.33; very low certainty in the evidence of effects) differ between the 2 groups.

Harms and burden. Rates of major bleeding may be similar (RR, 1.05; 95% CI, 0.32-3.40; low certainty in the evidence of effects), corresponding to 0 fewer (5 fewer to 17 more) events per 1000 patients. We were unable to estimate the RR of major reoperation given that there were no events in either group in the 2 included trials.[107,117]

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone. The panel was unable to assess the impact of adding mechanical prophylaxis on the risk of other outcomes, such as falls or skin complications. These might be considered "unmeasured harms" of mechanical prophylaxis. The panel judged the costs associated with combined prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. Cost-effectiveness probably favors combined pharmacological and mechanical prophylaxis. There would probably be no impact on health equity; combined pharmacological and mechanical prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel determined that there was very low certainty evidence for a net health benefit/harm for combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone. Most of the evidence evaluating this question comes from the orthopedic (joint arthroplasty) setting.

Conclusions and research needs for this recommendation. The guideline panel suggests using combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone for patients undergoing major surgery, based on very low certainty in the evidence of effects. The panel judged that combined pharmacological and mechanical prophylaxis would be most beneficial for patients considered at very high risk for VTE following major surgery.

Further high-quality research studies using clinically important outcomes comparing combination pharmacological and mechanical methods with pharmacological methods alone are required to provide greater certainty about this recommendation. Studies addressing this question outside the orthopedic setting are most needed.

Question: Should mechanical prophylaxis combined with pharmacological prophylaxis vs mechanical prophylaxis alone be used for patients undergoing major surgery?

Recommendation 5

For patients undergoing major surgery, the ASH guideline panel *suggests* using combined mechanical and pharmacological prophylaxis or mechanical prophylaxis alone, depending on the risk of VTE and bleeding based on the individual patient and the type of surgical procedure (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).
Remark: For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Summary of the evidence. We identified 7 systematic reviews addressing, in part, this question.[23-26,29,32,33] We identified 19 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.[36,60,62,68,118-132] Our systematic search of RCTs identified 5 additional studies that fulfilled the inclusion criteria.[70,72,133-136]

Fourteen studies reported the effect of combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone on the risk of mortality.[36,60,62,68,120,121,124,125,127,128,130,133,134,136] Sixteen studies reported the effect on the development of symptomatic PEs,[60,62,70,120-131,134] and 11 studies reported on the effect on any PEs[36,118,120,121,126,128,130,131,133,135,136] Six studies reported data on symptomatic DVTs,[62,70,120,127,128,131] and 10 studies reported data on any proximal DVT.[62,70,120-122,124,125,127,128,130] Five studies reported data on symptomatic distal DVTs,[70,120,127,128,131] and 14 studies reported on any distal DVT.[118,120-122,124,125,127,128,130] Fifteen studies reported the effect of combined mechanical and pharmacological prophylaxis on the risk of major bleeding,[60,62,68,118,119,121,123-125,127,128,130,134-136] and 4 studies reported the effect on the risk of reoperation.[118,125,134,135]

The EtD framework is available online at https://guidelines.gradepro.org/profile/75138F44-7AFE-A008-A8BD-10DD1DFD5377.

Benefits. There is likely no difference in mortality between combined prophylaxis and mechanical prophylaxis alone (RR, 1.24; 95% CI, 0.67-2.30; moderate certainty in the evidence of effects), corresponding to 3 more (4 fewer to 17 more) deaths per 1000 patients. There is likely a reduction in symptomatic PEs (RR, 0.34; 95% CI, 0.13-0.90; moderate certainty in the evidence of effects) favoring combined prophylaxis. Depending on the baseline risk, assumed to be 0.8% or 1.1% based on a large observational study,[73] this benefit likely corresponds to 5 fewer (1-7 fewer) per 1000 patients in a lower-risk population to 7 fewer (1-10 fewer) per 1000 patients in a higher-risk population. The risk of symptomatic proximal DVT (RR, 0.71; 95% CI, 0.07-6.75; low certainty in the evidence of effects) and symptomatic distal DVT (RR, 0.38; 95% CI, 0.06-2.42; low certainty in the evidence of effects) may be similar between the 2 interventions, irrespective of the baseline risk group.

Harms and burden. Combined prophylaxis likely results in a small increased risk for major bleeding (RR, 2.23; 95% CI, 1.09-4.57; moderate certainty in the evidence of effects). This likely corresponds to 14 more (1-42 more) per 1000 patients. Rates of major reoperation may be similar (RR, 2.96; 95% CI, 0.73-12.05; low certainty in the evidence of effects) between the 2 interventions, corresponding to 4 more (1 fewer to 21 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and imprecision.

Other EtD criteria and considerations. The panel judged that the balance between desirable and undesirable effects does not favor combined pharmacological and mechanical prophylaxis vs mechanical prophylaxis alone. Instead, the balance between desirable and undesirable effects will depend upon the risk of VTE and bleeding based on the individual patient and the type of surgical procedure. The panel judged the costs associated with combined prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. Cost-effectiveness varies based on the underlying VTE and bleeding risk categories. There would probably be no impact on health equity, and combined prophylaxis and mechanical prophylaxis alone would be acceptable to stakeholders and probably feasible to implement.

Conclusions and research needs for this recommendation. The guideline panel suggests using combined mechanical and pharmacological prophylaxis or mechanical prophylaxis alone for patients undergoing major surgery (based on low certainty in the evidence of effects). The balance of effects was considered dependent upon the risk of VTE and bleeding. Therefore, it is important to establish the baseline risk for VTE and major bleeding in surgical patients. For patients considered at high thrombosis risk and low bleeding risk, combined mechanical and pharmacological prophylaxis should be considered. For patients at high bleeding risk, mechanical prophylaxis methods alone may be preferred.

Further high-quality research studies using clinically important outcomes to identify patients with high baseline risk for VTE in whom combined pharmacological and mechanical prophylaxis would be of value, particularly outside the orthopedic setting, are needed.

Prophylactic insertion of an IVC filter. *Question: Should insertion of an IVC filter vs no IVC filter be used for VTE prophylaxis for patients undergoing major surgery?*

Recommendation 6

For patients undergoing major surgery, the ASH guideline panel *suggests against* using IVC filters for prophylaxis of VTE (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 2 systematic reviews of RCTs and observational studies[137,138] that addressed this research question in bariatric surgery and trauma patients. We identified 14 studies[139-152] in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our search for RCTs and observational studies identified 1 additional study that fulfilled the inclusion criteria.[153] Additionally, we identified 1 systematic review of RCTs and

observational studies that was published after our initial literature search, which did not include any new study not already included in our meta-analysis.[154] We also identified 1 RCT published in July 2019, evaluating the use of IVC filters for patients experiencing trauma.[155] Although we did not update the meta-analysis, the trial results were assessed by the panel as consistent with the recommendation.

Of the 15 studies included in the meta-analysis, 1 was an RCT.[150] Twelve of the studies reported the effect of IVC filters on the risk of mortality.[139,143-147,149-153] Five studies assessed the development of symptomatic PEs,[142,149,150,152,153] and 10 studies assessed the development of any PE.[139-141,143-148,151] Ten studies assessed the development of DVTs,[139,141,143,144,146-148,150,151,153] with 1 study assessing the development of symptomatic DVTs specifically[141] and 1 study assessing the development of proximal DVTs specifically.[153]

The EtD framework is available online at https://guidelines.gradepro.org/profile/4885EDB9-B445-5554-BD62-CFE2EED6D08E.

Benefits. IVC filter use may increase mortality slightly (RR, 1.38; 95% CI, 0.81-2.37; very low certainty in the evidence of effects), although the confidence interval was wide and included the possibility of no increase. Overall, we are very uncertain of this finding. Based on the control group event rate of 1.1% in this meta-analysis, this would correspond to 4 more deaths (2 fewer to 15 more) per 1000 patients receiving an IVC filter following major surgery or trauma. IVC filters may reduce the risk of symptomatic PE following major surgery and trauma (RR, 0.29; 95% CI, 0.11-0.80; very low in the evidence of effects), but we are very uncertain about this finding. Based on a baseline risk of 0.8% from observational data,[73] this corresponds to 6 fewer (2-7 fewer) symptomatic PEs. Based on a higher baseline risk of 1.1%,[73] this could result in 8 fewer PEs (2-10 fewer) per 1000 patients receiving an IVC filter; however, this is very uncertain. Rates of symptomatic proximal DVT may be increased with use of IVC filters (RR, 2.19; 95% CI, 1.07-4.50; very low certainty in the evidence of effects), but we are once again very uncertain of this finding. This corresponds to 20 more (1-58 more) or 31 more (2-92 more) per 1000 patients, based on baseline risks of 1.6% and 2.6%, respectively, from observational data.[73] We are also uncertain whether rates of symptomatic distal DVT are increased (RR, 2.72; 95% CI, 1.41-5.21; very low certainty in the evidence of effects), corresponding to 2 more (1-6 more) to 4 more (1-9 more) per 1000 patients, based on baseline risks of 0.1% and 0.2%, respectively, from observational data.[73]

Harms and burden. The panel did not consider potential harms of IVC filters beyond VTE. These potential harms would include potentially severe complications, such as IVC perforation and IVC filter embolization.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, inconsistency, and indirectness.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals might value the main outcomes. They judged that the balance between desirable and undesirable effects favored not using IVC filters in the setting of major surgery or trauma. The panel judged from our analysis of data, largely from observational studies, that the high rates of DVT and the trend for higher mortality associated with the use of IVC filters outweighed the potential reduction in PEs. Furthermore, a recently published high-quality RCT of IVC filters, following major trauma for patients in whom pharmacological prophylaxis was considered contraindicated, did not find that IVC filters reduced symptomatic PE or death.[155] Given there are serious nonthrombotic risks associated with IVC filters (eg, IVC perforation and IVC filter embolization) that were not considered in our analysis, this would further strengthen our recommendation against IVC filter use.[156]

The panel also recognized that the cost of IVC filters and resources associated with their insertion were large. The panel concluded that routine use of IVC filters following major surgery or trauma was probably not cost-effective and favored not placing a filter. Because of the increased resources required, high costs, and limited availability of interventional radiology units, health equity would probably be reduced by use of IVC filters. Routine use of IVC filters might also not be acceptable or feasible to implement for some stakeholders.

Conclusions and research needs for this recommendation. The panel suggests against using IVC filters for prophylaxis of VTE for patients undergoing major surgery or trauma patients based upon very low certainty in the evidence. The very low quality evidence underlying this recommendation supports the need for well-designed RCTs evaluating clinically important outcomes to better define the role of IVC filters for patients who cannot safely or feasibly receive pharmacological or mechanical prophylaxis following major surgery or trauma. Further studies quantifying the nonthrombotic risks of IVC filters would also be of value.

Timing of antithrombotic prophylaxis

Question: Should extended antithrombotic prophylaxis vs short-term antithrombotic prophylaxis be used for patients undergoing major surgery?

Recommendation 7

For patients undergoing major surgery, the ASH guideline panel *suggests* using extended antithrombotic prophylaxis over short-term antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Extended prophylaxis was generally considered as beyond 3 weeks (range: 19-42 days), and short-term prophylaxis was considered as up to 2 weeks (range: 4-14 days).

Summary of the evidence. We identified 9 systematic reviews addressing this research question.[157-165] We identified 14 studies[166-179] in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search of RCTs identified 6 additional studies[180-185] not included in previous systematic reviews that fulfilled the inclusion criteria.

Seventeen studies reported the effect of extended vs short-term duration of pharmacological thromboprophylaxis on the development of mortality,[166,167,170-173,175-185] 17 studies reported the effect on the development of PEs,[166,167,170-184] 18 studies reported the effect on the development of proximal DVTs,[166-173,175-184]

14 studies reported the effect on the development of distal DVTs,[166,169,171-173,175,177-184] 16 studies reported the effect on the risk of major bleeding,[167-173,177-185] and 6 studies reported the effect on the risk of reoperation.[166,173,174,179,184,185] In general, these studies compared shorter courses of pharmacological prophylaxis (4-14 days) with extended courses of pharmacological prophylaxis (19-42 days) and then followed patients for a common period (3-9 months) for VTE and bleeding complications.

The EtD framework is available online at https://guidelines.gradepro.org/profile/79bce70d-c689-4fbf-b0e4-c2ec3142bb2c.

Benefits. There is likely no difference in mortality between extended- and standard-course antithrombotic prophylaxis (RR, 0.94; 95% CI, 0.64-1.39; moderate certainty in the evidence of effects); this corresponds to 1 fewer death (6 fewer to 6 more) per 1000 patients. There is likely a small reduction in symptomatic PEs (RR, 0.44; 95% CI, 0.22-0.85; moderate certainty in the evidence of effects). Depending on baseline risk,[73] this corresponds to 4 fewer (1-6 fewer) deaths per 1000 patients with a baseline risk of 0.8% and 6 fewer (2-9 fewer) deaths per 1000 patients with a baseline risk of 1.1% receiving extended pharmacological prophylaxis. Symptomatic proximal DVTs are also likely reduced (RR, 0.30; 95% CI, 0.21-0.42; moderate certainty in the evidence of effects). Depending upon the baseline risk,[73] this corresponds to 12 fewer (10-13 fewer) symptomatic proximal DVTs per 1000 patients in a lower-risk group of patients with a 1.6% baseline risk or 18 fewer (15-21 fewer) per 1000 patients in a higher-risk group with a 2.6% baseline risk. Extended pharmacological prophylaxis likely reduces distal DVTs (RR, 0.57; 95% CI, 0.37-0.87; moderate certainty in the evidence of effects), which corresponds to 1 fewer (0-1 fewer) symptomatic distal DVT per 1000 patients based on a 0.1% baseline risk from observational data.[73]

Harms and burden. Rates of major bleeding may be similar (RR, 1.00; 95% CI, 0.59-1.70; low certainty in the evidence of effects), corresponding to 0 fewer (3 fewer to 6 more) per 1000 patients. Rates of reoperation may also be similar (RR, 0.82; 95% CI, 0.34-1.99; very low certainty in the evidence of effects), but we are very uncertain about this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors extended-duration vs standard-duration prophylaxis. The panel judged the costs associated with extended-duration prophylaxis to be moderate based on very low certainty in the evidence. Cost-effectiveness probably favors extended-duration prophylaxis. Health equity is possibly reduced with extended-duration prophylaxis, with economically disadvantaged patients potentially being unable to afford the required medications or medication copayments. Extended-duration prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel recognized that most of the trials compared a prolonged prophylaxis (up to 42 days, or ~6 weeks following surgery) with a short duration of anticoagulant prophylaxis designed to approximate the length of a postoperative hospital stay (~4-14 days) in the eras in which the studies were performed. Furthermore, the panel recognized that these studies were largely limited to 2 high-risk surgical scenarios (total hip or knee arthroplasty and major cancer general surgical procedures).

Conclusions and research needs for this recommendation. The guideline panel determined that the net benefit favored using extended-course antithrombotic prophylaxis over short-term antithrombotic prophylaxis for patients undergoing major surgery based on very low certainty evidence. Given the very low certainty in the evidence of effects this is based upon, there is a critical need for higher-quality studies comparing extended vs short-term prophylaxis using clinically important outcomes in contemporary surgical practices, which are marked by early patient mobilization and shorter hospital stays. There is particularly a need for studies outside the general hip and knee arthroplasty and cancer general surgical settings to confirm the benefits of extended prophylaxis in other settings. There also appears to be a need for further research to determine the optimal duration of extended prophylaxis.

Question: Should early vs delayed antithrombotic prophylaxis be used for patients undergoing major surgery?

Recommendation 8

For patients undergoing major surgery, the ASH guideline panel *suggests* using early or delayed antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Twelve hours following surgery was arbitrarily selected to be the cutoff point between early and late postoperative antithrombotic administration.

Summary of the evidence. We did not find any systematic reviews that addressed this question. In our systematic search of the literature we found 6 studies that fulfilled our inclusion criteria and measured outcomes relevant to this context.[186-191] We cross-referenced the studies found in our search with the references from a recent narrative review[192] but did not identify any additional studies that fulfilled our inclusion criteria. All studies included surgical patients. Twelve hours was selected to be the cutoff point between early and late postsurgical antithrombotic administration. Six studies[186-191] reported the effect of early vs late postsurgical antithrombotic administration on the risk of mortality and on the risk of development of any PEs. Five studies[186,188-191] reported the effect on the risk of any proximal and any distal DVTs, and 1 reported the effect on the risk of any DVT.[187] Only the 5 studies that specified the location of the DVT were included in the evidence profile. Six studies[186-191] reported the effect of early vs late postsurgical antithrombotic administration on the risk of major bleeding and on the risk of reoperation.

The EtD framework is available online at https://guidelines.gradepro.org/profile/E664E38D-FA7C-DBC9-8E77-373D0582050E.

Benefits. Early prophylaxis may result in no difference in mortality (RR, 1.57; 95% CI, 0.77-3.19; very low certainty in the evidence of effects), but we are very uncertain about this finding. This corresponds to 1 more (1 fewer to 6 more) per 1000 patients. We are uncertain about the effect of early prophylaxis on

symptomatic PEs (RR, 0.63; 95% CI, 0.23-1.72; very low certainty in the evidence of effects); depending on the baseline risk from observational data,[73] this corresponds to 3 fewer (6 fewer to 6 more) to 4 fewer (8 fewer to 8 more) per 1000 patients with baseline risks of 0.8% and 1.1%, respectively. We are also uncertain of the effect of early prophylaxis on symptomatic proximal DVTs (RR, 0.88; 95% CI, 0.40-1.96; very low certainty in the evidence of effects), corresponding to 2 fewer (10 fewer to 16 more) to 3 fewer (16 fewer to 25 more) per 1000 patients when applying baseline risks of 1.6% and 2.6%, respectively.[73] Early prophylaxis has an uncertain effect on distal DVTs (RR, 0.68; 95% CI, 0.41-1.12; very low certainty in the evidence of effects), with an absolute risk reduction from 0 fewer (0-1 fewer; baseline risk, 0.1%[73]) to 1 fewer (0-1 fewer; baseline risk, 0.2%[73]) symptomatic distal DVT per 1000 patients.

Harms and burden. The risk of major bleeding may be similar (RR, 1.63; 95% CI, 0.81-3.29; very low certainty in the evidence of effects), corresponding to 5 fewer (1 fewer to 17 more), although we are very uncertain of this finding. Also, the need for reoperation may be increased (RR, 1.84; 95% CI, 0.89-3.80; very low certainty in the evidence of effects) corresponding to 2 more reoperations (0 fewer to 6 more) per 1000 patients. Once again, we are very uncertain about this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes and downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. Based on very low certainty in the evidence of effects, the panel judged that the balance of effects did not favor early or delayed institution of pharmacological antithrombotic prophylaxis in major surgical patients. Costs and saving would likely be negligible, and the panel saw no particular issues related to equity, acceptability, or feasibility.

Conclusions and research needs for this recommendation. The guideline panel *suggests* early administration (postoperative, within 12 hours) or late administration (postoperative, after 12 hours) of antithrombotic prophylaxis in major surgical patients, based on very low certainty in the evidence of effects. In light of the very low certainty in the evidence of effects, further high-quality studies using clinically important outcomes are important to provide greater certainty about the benefits and risks of early pharmacological prophylaxis. The panel was particularly interested in seeing future high-quality studies of early vs late pharmacological prophylaxis studies in high-risk bleeding patients, examining the benefits and risks of later intervention (days following surgery) once the bleeding risk had greatly subsided.

Orthopedic surgery

Question: Should ASA vs anticoagulants be used for patients undergoing total hip or knee arthroplasty?

Recommendation 9

For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using ASA or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We found 7 RCTs that compared the use of ASA vs anticoagulants for patients undergoing total hip arthroplasty or total knee arthroplasty.[193-199] Additionally, we identified 2 trials comparing ASA with LMWH in total hip arthroplasty patients[200] and ASA with DOAC in total hip arthroplasty or total knee arthroplasty patients,[201] in which all participants received a 10-day period of LMWH or a 5-day period of DOACs, respectively, prior to randomization. The trials were reviewed by the panel but were not included in the main meta-analysis because of differences in the comparator groups. Of the 7 studies included in the analysis, 2 studies compared ASA with UFH,[193,195] 4 studies compared ASA with LMWH,[194,196,198,199] and 2 studies compared ASA with oral anticoagulants.[197,199] All 7 studies reported the outcomes of mortality and PE,[193-199] 6 studies reported on proximal and distal DVTs,[195-199] and 5 studies reported on major bleeding.[194-196,198,199] We found no studies addressing the outcome of reoperation.

The EtD framework is available online at https://guidelines.gradepro.org/profile/3532ED1D-6A40-A982-BC3F-6DA318B3B611.

Benefits. There may be no difference in mortality between ASA and anticoagulants (RR, 2.32; 95% CI, 0.15-36.90; low certainty in the evidence of effects). There also may be no difference in the risk of symptomatic PEs between ASA and anticoagulants (RR, 1.49; 95% CI, 0.37-6.09; very low certainty in the evidence of effects), corresponding to 3 more (4 fewer to 29 more) symptomatic PEs per 1000 patients based on a baseline risks of 0.6%[202,203] from observational data; however, we are very uncertain of this finding. There also may be no difference in the risk of proximal DVTs (RR, 1.49; 95% CI, 0.51-4.34; very low certainty in the evidence of effects), corresponding to 3 more symptomatic (3 fewer to 30 more) proximal DVTs per 1000 patients based on a baseline risk of 0.6%,[202,203] or in the risk of distal DVTs (RR, 1.45; 95% CI, 0.86-2.46; very low certainty in the evidence of effects), corresponding to 0 fewer symptomatic distal DVTs (0 fewer to 1 more) per 1000 patients based on a baseline risk of 0.05%,[202,203] although we were very uncertain about both findings.

Harms and burden. ASA may lead to a small increased risk for major bleeding (RR, 2.63; 95% CI, 0.64-10.79; low certainty in the evidence of effects). These findings correspond to 6 more (1 fewer to 35 more) major bleeding events per 1000 patients. We found no evidence to inform the comparative risk of reoperation.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel determined that there was probably important uncertainty or variability in how much affected individuals value the main outcomes. It further judged that use of ASA saved costs and resources; however, the results of cost-effectiveness studies varied, with some favoring ASA and others favoring anticoagulant prophylaxis. Health equity would probably be increased as a consequence of the use of ASA. Acceptability was thought to also vary depending on the type of stakeholder (patient vs health care provider). There were no concerns about the feasibility of implementation. A recent large RCT supports our recommendation that ASA or anticoagulants be used for VTE prophylaxis following total hip or knee arthroplasty. However, this study was not included in our analysis

because all patients received a 5-day course of a DOAC before being randomized to ASA or to stay on a DOAC for extended prophylaxis.[201]

Conclusions and research needs for this recommendation. The guideline panel suggests using ASA or anticoagulants for patients undergoing total hip arthroplasty or total knee arthroplasty (conditional recommendation based on very low certainty in the evidence of effects). They determined that there was very low certainty evidence for any net health benefit/harm from using ASA vs anticoagulants. Of 8 panel members who voted on this recommendation, 5 voted for recommending either intervention, and 3 voted for a conditional recommendation in favor of anticoagulants.

The panel identified that there is a need for large well-designed clinical trials using clinically important end points comparing ASA with other pharmacological methods following total hip and knee arthroplasty. The panel noted that such studies are underway.

Question: Should DOACs vs LMWH be used for patients undergoing total hip or knee arthroplasty?

Recommendation 10

For patients undergoing total hip arthroplasty or total knee arthroplasty in which anticoagulants are used, the ASH guideline panel *suggests* using DOACs over LMWH (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Summary of the evidence. We identified 1 systematic review[204] that addressed this question. Twenty-two studies in this review fulfilled our inclusion criteria. Our update of the systematic review identified 16 additional studies. All studies included patients undergoing elective hip or knee replacement.

Five studies assessed the effects of dabigatran,[191,205-208] 15 studies assessed the effects of rivaroxaban,[180,185,189,190,199,209-218] 4 studies assessed the effects of apixaban,[219-222] 5 studies assessed the effects of darexaban[223-226] and edoxaban,[227-231] and 4 studies assessed the effects of other DOACs.[232-235]

Thirty-four studies reported mortality,[180,185,189-191,199,205-215,218-222,224-231,233-235] whereas 33 studies reported nonfatal PEs.[180,185,189-191,199,205-212,214-216,219-222,224-231,233-235] We estimated proximal and distal DVTs using the pooled estimate from symptomatic DVTs, which was reported in 30 studies.[185,189-191,199,205-212,214-216,219-222,224-230,234,235] Thirty-two studies reported major bleeding,[180,185,189-191,205-212,214,215,219-222,224-235] whereas only 15 studies reported bleeding leading to reoperation.[180,185,189-191,205-207,209-212,215,220,221]

We tested potential differences in the effects with specific drugs and between classes (anti–factor IIa vs anti–factor Xa). We found no interaction for any of the outcomes. Additionally, we conducted a sensitivity analysis excluding dose-finding studies. The results did not change appreciably.

The EtD framework is available online at https://guidelines.gradepro.org/profile/9160FAA2-4F98-A3AA-9816-64DF796ABBC7.

Benefits. DOACs probably do not reduce mortality compared with that associated with LMWH (RR, 0.94; 95% CI, 0.53-1.66; moderate certainty in the evidence of effects); this corresponds to 0 fewer deaths (1 fewer to 1 more) per 1000 patients. DOACs probably slightly reduce the rate of symptomatic PEs (RR, 0.74; 95% CI, 0.50-1.10; moderate certainty in the evidence of effects); based on a baseline risk of 0.6% from observational data,[202,203] this corresponds to 1 fewer (3 fewer to 1 more) symptomatic PE per 1000 patients. The use of DOACs reduces symptomatic proximal DVTs slightly (RR, 0.56; 95% CI, 0.39-0.79; high certainty in the evidence of effects), which corresponds to 3 fewer (1-4 fewer) symptomatic proximal DVTs per 1000 patients, based on a baseline risk of 0.6% from observational data.[202,203] This effect on symptomatic distal DVTs is probably not clinically relevant (RR, 0.56; 95% CI, 0.39-0.79; high certainty in the evidence of effects), which corresponds to 0 fewer symptomatic distal DVTs per 1000 patients based on a baseline risk of 0.049%, from observational data.[202,203]

Harms and burden. DOACs probably do not increase major bleeding compared with LMWH (RR, 1.03; 95% CI, 0.79-1.35; moderate certainty in the evidence of effects), which corresponds to 0 fewer major bleeding events (2 fewer to 4 more) per 1000 patients. Similarly, rates of reoperation may not be meaningfully increased (RR, 1.43; 95% CI, 0.75-2.71; moderate certainty in the evidence of effects) given the low event rates; this corresponds to 0 fewer reoperations (0 fewer to 2 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as moderate based on the lowest certainty in the evidence for the critical outcomes, downgrading for imprecision.

Other EtD criteria and considerations. The panel judged the desirable and undesirable effects as being small and trivial, respectively, in magnitude. Cost-effectiveness was judged to probably favor the use of DOACs. Similarly, equity, acceptability, and feasibility each favored the use of DOACs and contributed to the recommendation in their favor. Use of out-of-hospital prophylaxis, which is routine following total hip or knee arthroplasty, particularly favored DOACs over LMWH, given the need for parenteral administration of the latter agent.

Conclusions and research needs for this recommendation. The guideline panel suggests using DOACs rather than LMWH for patients undergoing total hip or knee arthroplasty. Based on an overall moderate certainty in the evidence of effects, the panel judged the balance of effects to probably favor the use of DOACs over LMWH. The ultimate judgment of a conditional recommendation for DOACs was based on anonymous voting by panel members without direct financial conflicts, with a majority of 5 voting for this recommendation (vs 4 in favor of a recommendation for using either). The panel recommended a need for large clinical trials using clinically relevant end points comparing different DOACs. Further studies regarding the optimal timing of the initiation of postoperative dosing of DOACs are warranted.

Question: Should 1 DOAC vs another DOAC be used for patients undergoing total hip or knee arthroplasty?

Recommendation 11

For patients undergoing surgery, the ASH guideline panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Summary of the evidence. We found no study that compared different classes of DOACs or individual DOACs of the same class head to head. Therefore, we used the body of evidence comparing DOAC prophylaxis vs LMWH (see recommendation 10) as the basis for an indirect assessment of their relative effectiveness.

The EtD framework is available online at https://guidelines.gradepro.org/profile/16A3927F-FB2D-C278-9FE5-D4535020FE27.

Benefits. In the absence of comparative trials of different classes of DOACs (anti–factor IIa vs anti–factor Xa) or individual DOACs of the same class, we tested potential differences by analyzing potential subgroup effects. Based on the tests for interaction, we did not demonstrate any evidence for a clinically relevant subgroup effect for any of the potentially desirable outcomes. Based on this finding, the panel assumed that the beneficial effects were likely similar for different DOACs.

Harms and burden. Similarly, based on tests for interaction, we did not find any evidence for a clinically relevant subgroup effect for any of the potentially undesirable outcomes. Based on this finding, the panel assumed that the undesirable effects were likely similar for different DOACs.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for indirectness and imprecision.

Other EtD criteria and considerations. Based on these findings, the panel judged that the balance of effects did not favor any particular DOAC over another. The panel also judged that issues surrounding cost-effectiveness, equity, acceptability, and feasibility also did not weigh in sufficiently to favor 1 DOAC over another.

Conclusions and research needs for this recommendation. Based on overall low certainty in the evidence of effects, the panel judged that there were no net benefits in favor of any DOAC vs another. Given the lack of direct comparative evidence, the panel identified an important need for high-quality head-to-head studies comparing different DOACs for the prevention of VTEs following total hip or knee arthroplasty.

Question: Should LMWH vs warfarin be used for patients undergoing total hip or knee arthroplasty?

Recommendation 12

For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review that addressed this question.[236] We identified 7 trials in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[39,219,237-241] Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria. Three studies were conducted with patients undergoing total hip arthroplasty,[39,239,241] 3 studies were conducted with patients undergoing total knee arthroplasty,[219,237,240] and 1 study addressed both populations.[238] Five studies[219,237-240] reported the effect of LMWH compared with warfarin on mortality, 5 studies reported the effect on the development of symptomatic PEs,[39,219,237,238,240] 6 studies reported on any proximal DVT,[219,237-241] and 2 studies reported on any distal DVT.[237,241] All 7 studies reported the effect on the risk of major bleeding,[39,219,237-241] and 2 studies reported on the risk of reoperation.[237,241]

The EtD framework is available online at https://guidelines.gradepro.org/profile/BC1783C1-D62B-AECB-B9F7-87A9D474A834.

Benefits. LMWH may result in little or no difference in mortality compared with warfarin (RR, 0.51; 95% CI, 0.14-1.88; low certainty in the evidence of effects). LMWH likely does not reduce symptomatic PEs (RR, 0.83; 0.27-2.54; moderate certainty in the evidence of effects). LMWH may reduce symptomatic proximal DVTs (RR, 0.61; 95% CI, 0.36-1.02; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 0.61; 95% CI, 0.42-0.88; low certainty in the evidence of effects). This corresponds to 2 fewer (0-4 fewer) symptomatic proximal DVTs and 0 fewer symptomatic distal DVTs with the use of LMWH than with warfarin for 1000 patients treated, based on baseline risks of 0.6% and 0.049%, respectively, from observational data.[202,203]

Harms and burden. LMWH use likely results in increased major bleeding compared with the use of warfarin (RR, 1.81; 95% CI, 1.31-2.50; moderate certainty in the evidence of effects). This corresponded to 16 more (5-22 more) major bleeds per 1000 patients. There was no difference with regard to reoperation rates between those receiving LMWH or warfarin (RR, 3.09; 95% CI, 0.13-75.48; moderate certainty in the evidence of effects), which corresponded to 0 more events per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel judged that there was possibly important uncertainty or variability in how much people value the main outcomes. The balance between desirable und undesirable effects probably favored LMWH. Resources requirements of warfarin were deemed moderate, particularly with regard to the need for, and the complexity of, anticoagulant monitoring, but cost-effectiveness data probably did not favor warfarin or LMWH. There probably would be no impact on health equity; both agents appear acceptable to stakeholders and are feasible to implement.

Conclusions and research needs for this recommendation. The guideline panel suggests using LMWH rather than warfarin for patients undergoing total hip arthroplasty or total knee arthroplasty. The guideline panel determined that there was very low certainty evidence for a net health benefit/harm from using LMWH rather than warfarin. Based on the body of available evidence, it is likely that warfarin reduces the risk of major bleeding based on evidence of moderate certainty. However, it may also increase the risk of proximal DVTs, based on very low quality evidence.

Further high-quality studies using clinically important outcomes would be of value to improve the certainty in the recommendation. However, given the availability of DOACs as oral agents that do not require anticoagulant monitoring or dose adjustment, further

clinical trials using warfarin are not regarded as a high priority at this time.

Question: Should LMWH vs UFH be used for patients undergoing total hip or knee arthroplasty?

Recommendation 13

For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel *suggests* using LMWH rather than UFH (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

Summary of the evidence. We identified 1 systematic review that addressed this question.[236] We identified 12 trials in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[242-253] Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria. Ten trials were performed on patients undergoing total hip arthroplasty,[242-244,246,247,249-253] and 2 trials were conducted on patients undergoing total knee arthroplasty.[245,248] Five trials reported the effect of LMWH compared with UFH on mortality,[244,247,249,251,252] 10 studies reported the effect on the development of symptomatic PEs,[242-245,247-249,251-253] 8 studies reported the effect on any proximal DVT,[242,244-249,251] and 6 studies reported the effect on any distal DVT.[242,244-249,251] Six studies reported the effect on the risk of major bleeding,[244,245,249-251,253] and 2 studies reported the effect on the risk of reoperation.[247,248]

The EtD framework is available online at https://guidelines.gradepro.org/profile/06FDBFB0-4D4E-E0D0-AEAD-C8B371DFA939.

Benefits. LMWH results in little or no difference in mortality compared with UFH (RR, 0.26; 95% CI, 0.03-2.36; high certainty in the evidence of effects), which corresponded to 3 fewer (4 fewer to 5 more) deaths per 1000 patients. LMWH probably reduces the risk of symptomatic PEs slightly (RR, 0.37; 95% CI, 0.19-0.71; moderate certainty in the evidence of effects). This corresponds to 4 fewer (2-5 fewer) symptomatic PEs per 1000 patients, based on a baseline risk of 0.6% from observational data.[202,203] LMWH also likely reduces the risk of symptomatic proximal DVTs (RR, 0.48; 95% CI, 0.34-0.69; moderate certainty in the evidence of effects), corresponding to 3 fewer (2-4 fewer) per 1000 patients, based on a baseline risk of 0.6% from observational data.[202,203] LMWH appears to result in little or no difference in symptomatic distal DVTs (RR, 1.18; 95% CI, 0.81-1.72; low certainty in the evidence of effects), with very small corresponding absolute effect size estimates based on a baseline risk of 0.049% from observational data.[202,203]

Harms and burden. LMWH likely results in a small decrease in the risk of major bleeding (RR, 0.55; 95% CI, 0.27-1.13; moderate certainty in the evidence of effects); this corresponds to 19 fewer (30 fewer to 5 more) major bleeds per 1000 patients. We were unable to estimate an effect on the risk of reoperation given that the included studies reported no events for this outcome.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as moderate based on the lowest certainty in the evidence for the critical outcomes, downgrading for imprecision.

Other EtD criteria and considerations. The panel determined that there was probably important uncertainty or variability in how much affected individuals value the main outcomes. Cost-effectiveness likely differs by country but probably favors LMWH. The panel assessed that this recommendation probably would have no impact on health equity and would be acceptable to stakeholders. LMWH is already widely used, and the panel had no concern about the feasibility of implementation.

Conclusions and research needs for this recommendation. The guideline panel recommends LMWH rather than UFH for patients undergoing total hip arthroplasty or total knee arthroplasty.

The guideline panel determined that there is moderate certainty evidence for a net health benefit/harm from using LMWH over UFH. Future large studies using clinically relevant end points would help to better inform this recommendation, although this research question would not be regarded as high priority.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing hip fracture repair?

Recommendation 14

For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review[254] that addressed, in part, this question. We identified 5 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[255-259] Our systematic search of RCTs identified 7 additional studies that fulfilled the inclusion criteria.[260-266] Nine studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of mortality.[255,256,258,259,261-265] Nine studies reported the effect on development of any PEs,[255-259,261,264-266] and 5 studies reported the effect of any proximal DVT and any distal DVT.[257,260,261,263,265] Eleven studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of major bleeding,[255,256,258-266] and 3 studies reported the effect on risk of reoperation.[258,261,266]

We tested potential differences in the effects with ASA and anticoagulant prophylaxis and performed a subgroup analysis. The analysis indicated no subgroup effect with regard to desirable and undesirable effects comparing ASA with anticoagulant prophylaxis. As a result, in this analysis, studies with ASA are pooled with those of anticoagulant prophylaxis compared with no pharmacological prophylaxis.

The EtD framework is available online at https://guidelines.gradepro.org/profile/A10CDC06-B411-D572-959A-A8405E1373A1.

Benefits. Pharmacological prophylaxis appears to result in little or no difference in mortality (RR, 0.95; 95% CI, 0.84-1.07; very low certainty in the evidence of effects), although we are very uncertain about this finding. This would correspond to 4 fewer deaths (11 fewer to 5 more) per 1000 patients based on a baseline risk of 7.1% from the control group event rate in the meta-analysis.

Pharmacological prophylaxis may reduce symptomatic PEs (RR, 0.49; 95% CI, 0.33-0.72; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 6 fewer (3-7 fewer) events per 1000 patients based on a baseline risk of 1.1% from the control group event rate in the meta-analysis. Based on lower baseline risk of 0.3% from observational data,[267] this would correspond to 2 fewer (1-2 fewer) symptomatic PEs per 1000 patients. Pharmacological prophylaxis may reduce symptomatic proximal DVTs (RR, 0.51; 95% CI, 0.38-0.69; very low certainty in the evidence of effects), but we are very uncertain of this finding. In a moderate-risk population with a baseline risk of 2.5%,[267] this corresponds to 12 fewer (8-16 fewer) per 1000 patients. Pharmacological prophylaxis likely has little or no effect on symptomatic distal DVTs (RR, 0.85; 95% CI, 0.56-1.29; very low certainty in the evidence of effects), but once again we are very uncertain of this finding.

Harms and burden. Pharmacological prophylaxis may increase major bleeding (RR, 1.24; 95% CI, 1.12-1.37; low certainty in the evidence of effects). Depending on baseline risk, this corresponds to 1 more (1-2 more) major bleed per 1000 patients in a lower-risk population (baseline risk of 0.5% from observational data)[267] or as many as 20 more (10-31 more) per 1000 patients in a higher-risk population (baseline risk of 8% from the control group event rate in the meta-analysis). Pharmacological prophylaxis appears to have little or no effect on the need for reoperation (RR, 1.05; 95% CI, 0.82-1.35; very low certainty in the evidence of effects); however, we are very uncertain of this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel judged the magnitude of the desirable effects as moderate in size and the undesirable effects as small in size. There was possibly important uncertainty or variability about how patients may value these outcomes. There would probably be no impact on equity, and the panel foresaw no issues with regard to acceptability and feasibility of using pharmacological prophylaxis in this patient population.

Conclusions and research needs for this recommendation. Although the overall certainty in the evidence of effects was very low, the panel judged that the balance of effects probably favored the use of pharmacological prophylaxis for VTE prophylaxis following hip fracture repair. Given the overall very low certainty in the evidence, the panel indicated that there remains an important need for large high-quality RCTs using clinically important end points to determine the optimal role of ASA or anticoagulant pharmacological prophylaxis in this patient population. However, higher priority would be comparative studies of different antithrombotic regimens for the prevention of VTEs in these patients requiring repair of hip fracture.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing hip fracture repair?

Recommendation 15

For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review[254] that addressed this question. We identified 3 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[268-270] Our update of the systematic review did not identify any additional study that fulfilled the inclusion criteria. Two studies reported the effect of LMWH prophylaxis compared with UFH prophylaxis on risk of mortality, as well as any proximal and distal DVTs,[268,269] and 3 studies reported the effect on any PEs and major bleeding.[268-270] No information on reoperation rates was available in any of the included studies.

The EtD framework is available online at https://guidelines.gradepro.org/profile/80C377E5-E3C0-36CD-B646-C2532AB4D4B9.

Benefits. LMWH appears to result in little or no difference in mortality compared with UFH prophylaxis following hip fracture repair (RR, 0.47; 95% CI, 0.10-2.12; very low certainty in the evidence of effects), although we are very uncertain about the effect. Assuming a baseline risk of 7.4% for UFH-treated patients, this would correspond to 39 fewer (66 fewer to 88 more) deaths per 1000 patients. We are very uncertain about the effect of LMWH on symptomatic PEs (RR, 2.13; 95% CI, 0.06-81.3; very low certainty in the evidence of effect). LMWH may result in a small, possibly unimportant, increase in symptomatic proximal DVTs (RR, 2.24; 95% CI, 0.92-5.43; low certainty in the evidence of effect) corresponding to 31 more (2 fewer to 111 more) per 1000 patients based on a baseline risk of 2.5% from observational data.[267] LMWH appears to result in little or no difference in symptomatic distal DVTs (RR, 0.66; 95% CI, 0.21-2.17; very low certainty in the evidence of effects).

Harms and burden. LMWH appears to result in little or no difference in major bleeding compared with UFH after hip fracture surgery (RR, 0.85; 95% CI, 0.19-3.79; very low certainty in the evidence of effects). This corresponds to 9 fewer (50 fewer to 173 more) major bleeds per 1000 moderate-risk patients with a baseline risk of 6.2% based on a lower baseline risk of 0.5% from observational data[267]; the corresponding absolute risk reduction would be 1 fewer (4 fewer to 14 more) per 1000 patients. No comparative information is available regarding the risks of reoperation following hip fracture with the use of LMWH or UFH.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects did not favor LMWH or UFH following hip fracture repair. The panel recognized the very low certainty in comparative evidence, which was based on three small RCTs that did not report symptomatic DVT outcomes. The panel recognized that the comparative resources associated with LMWH and UFH prophylaxis were probably negligible. Cost-effectiveness was considered to favor LMWH based upon results of a single study.[271] Using LMWH or UFH would probably not impact health equity, and either drug was deemed to be probably acceptable to stakeholders and feasible to implement.

Conclusions and research needs for this recommendation. Taking into consideration the very low certainty in the evidence, the panel judged that LMWH or UFH prophylaxis could be

recommended following hip fracture repair. Large RCTs using clinically important outcomes are needed to better define the relative benefits and risks of LMWH compared with UFH following hip fracture surgery.

Major general surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major general surgery?

Recommendation 16

For patients undergoing major general surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Summary of the evidence. We identified a systematic review of RCTs[272] addressing this research question. We identified 3 studies[273-275] in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search for RCTs identified 32[49,122,125,131,274,276-302] additional studies that fulfilled the inclusion criteria, including patients undergoing major general surgery. Sixteen studies[122,125,274-278,284,285,291,293,296,297,299,300,302] reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on the risk of mortality, and 11 studies[125,273,276-279,285,286,289,293,295] reported the effect on the development of symptomatic PEs. Six studies[49,125,278,285,287,290] reported the effect on development of screening-detected proximal DVTs, and 6 studies[124,277,283,284,286,289] reported the effect on development of screening-detected distal DVTs.

Twelve studies[125,273-276,282,285,287,293,295,297,298] reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of major bleeding, and 3 studies[275,282,295] reported the effect on risk of reoperation.

The EtD framework is available online at https://guidelines.gradepro.org/profile/3B5A5678-B1D9-4D60-8E1F-F3AD700132F8.

Benefits. Pharmacological prophylaxis compared with no pharmacological prophylaxis probably reduces mortality (RR, 0.76; 95% CI, 0.61-0.93; moderate certainty in the evidence of effects). This finding corresponds to 4 fewer deaths (1-7 fewer) per 1000 patients undergoing major general surgery. Pharmacological prophylaxis probably also reduces symptomatic PEs (RR, 0.45; 95% CI, 0.23-0.88; moderate certainty in the evidence of effects). This corresponds to 4 fewer (1-6 fewer) pulmonary embolic events per 1000 patients undergoing major general surgery. Pharmacological prophylaxis may also reduce symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 10 fewer (0-14 fewer) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 1.6% from observational data.[73] It may reduce symptomatic distal DVTs (RR, 0.57; 95% CI, 0.36-0.90; low certainty in the evidence of effects), which corresponds to 1 fewer (0-1 fewer) symptomatic distal DVT per 1000 patients undergoing major general surgery based on a baseline risk of 1.6% from observational data.[73]

Harms and burden. Pharmacological prophylaxis probably increases major bleeding (RR, 1.37; 95% CI, 0.89-2.13; moderate certainty in the evidence of effects). This corresponds to 10 more (3 fewer to 29 more) major bleeding events per 1000 patients undergoing major general surgery. Pharmacological prophylaxis results in little or no difference in reoperation (RR, 0.75; 95% CI, 0.21-2.77; low certainty in the evidence of effects).

Certainty in the evidence of effects. The overall certainty of the estimates of effects was based on the low certainty outcomes and was not based on the lowest certainty of evidence for the critical outcomes. In this case, the recommendation was sufficiently supported by the favorable impact on desirable effects for which there was higher quality evidence.

Other EtD criteria and considerations. The panel judged the desirable effects to be of moderate magnitude and the undesirable effects to be of small magnitude. They assumed that there was possibly important uncertainty or variability in patients' values. Pharmacological prophylaxis probably would incur moderate additional costs but was judged to be probably cost-effective. Pharmacological prophylaxis would probably have no impact on equity, was probably acceptable, and was likely feasible.

Conclusions and research needs for this recommendation. The panel judged that the overall balance of effects favored pharmacological prophylaxis over no pharmacological prophylaxis for patients undergoing major general surgery based on low certainty in the evidence of effects. Further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to these recommendations. However, such studies would not be considered as high priority by the panel.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing major general surgery?

Recommendation 17

For patients undergoing major general surgery, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 2 systematic reviews of RCTs[272,303] addressing this research question. We identified 40 studies[304-343] in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search for RCTs identified 6 additional studies[295,344-348] that fulfilled the inclusion criteria. Thirty studies reported the effect of LMWH vs UFH on risk of mortality.[305,307,308,310-312,314,317-319,321,322,325-327,329-339,341,342,346,347] Thirty-one studies reported the effect of LMWH vs UFH on development of symptomatic PEs,[295,305-306,310-312,314-319,321,322,324,326-335,337,339,344-346] 5 studies reported the effect on symptomatic proximal DVTs,[306,316,326,334,336] and 7 reported the effect on symptomatic distal DVTs.[306,316,326,329,334,336,341] Thirty-four studies reported the effect of LMWH vs UFH on risk of major bleeding,[295,305-307,311,313,315-319,321-339,341,344-346] and 16 studies reported the effect on risk of reoperation.[305,307,309,317,319,322,323,326,329,330,333-337,341]

The EtD framework is available online at https://guidelines.gradepro.org/profile/EF7ADEA0-49F1-7E89-A0DB-DE7A9E854A2B.

Benefits. Prophylaxis with LMWH vs UFH probably does not reduce mortality following major general surgery (RR, 1.03; 95% CI, 0.89-1.18; moderate certainty in the evidence of effects). We are very uncertain about the effect of LMWH on symptomatic PEs compared with that of UFH (RR, 0.83; 95% CI, 0.58-1.19; very low certainty in the evidence of effects), which corresponds to 1 fewer (3 fewer to 2 more) symptomatic PE per 1000 patients undergoing major general surgery based on a baseline risk of 0.8% from observational data.[73] It also appears to result in little or no difference in symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.00; very low certainty in the evidence of effects) or a reduction in symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects). We are very uncertain about the last 2 findings.

Harms and burden. Prophylaxis with LMWH vs UFH probably does not affect major bleeding (RR, 0.97; 95% CI, 0.78-1.20; moderate certainty in the evidence of effects). This corresponds to 0 fewer (3 fewer to 3 more) major bleeding events per 1000 patients undergoing major general surgery. LMWH probably results in little or no difference in reoperations (RR, 0.79; 95% CI, 0.57-1.08; moderate certainty in the evidence of effects), which corresponds to 3 fewer (6 fewer to 1 more) reoperations per 1000 patients undergoing major general surgery.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious inconsistency.

Other EtD criteria and considerations. There was possibly important uncertainty or variability in how patients valued the outcomes. Potential costs and savings were deemed of negligible relevance, assuming only in-hospital short-term prophylaxis. There was probably no impact on equity, because both LMWH and UFH were thought to be acceptable and feasible to implement. If extended prophylaxis beyond hospital discharge is planned, LMWH may be preferable given its once-daily dosing. The panel thought that both treatment options are already widely used and there should be few issues with implementation.

Conclusions and research needs for this recommendation. The guideline panel judged that the net benefit did not favor LMWH or UFH prophylaxis for patients undergoing major general surgery. Based on a very low overall certainty in the evidence, the panel determined that the balance of effects did not favor LMWH or UFH. In light of the very low certainty in the evidence, further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to this recommendation. However, such comparative studies are not regarded as high priority at this time.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing laparoscopic cholecystectomy?

Recommendation 18

For patients undergoing laparoscopic cholecystectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients with other risk factors for VTEs (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.[30] We identified 2 studies[118,349] in that review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the relative paucity of studies on patients undergoing laparoscopic cholecystectomy, data across major general, major gynecological, and major urological procedures were pooled, and laparoscopic cholecystectomy-specific baseline risk estimates were applied.[350] Five studies[66,294,301,351,352] were conducted on patients undergoing major gynecological surgery. Thirty-one[49,122,125,131,275-279,281-293,295-300,302] studies were conducted on patients undergoing major general surgery. Two studies[118,349] were conducted on patients undergoing laparoscopic cholecystectomy. Six studies[38,280,353-356] were conducted on patients undergoing urological surgery. Eighteen studies[122,125,274-278,284,285,291,293,296,297,299,300,302,353,354] reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of mortality, 16 studies[38,118,125,273,276-279,285,286,289,293,295,354-356] reported the effect on risk of symptomatic PEs, 6 studies[49,125,278,285,287,290] reported the effect on risk of screening-detected proximal DVTs, and 7 studies[66,125,278,284,285,287,290] reported the effect on risk of screening-detected distal DVTs. Fifteen studies[118,125,273-275,277,282,285,287,293,295,297,298,349,354] reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of major bleeding, and 6 studies[38,118,275,282,295,354] reported the effect on risk of reoperation.

The EtD framework is available online at https://guidelines.grade-pro.org/profile/E753AE97-D04A-D35F-ABE1-F9CAB9461DD1.

Benefits. Pharmacological prophylaxis probably results in a small unimportant reduction in overall mortality (RR, 0.75; 95% CI, 0.61-0.93; low certainty in the evidence of effects). This corresponds to 2 fewer (0-2 fewer) deaths per 1000 patients based on a baseline risk of 0.6% from observational data.[357] It may not reduce symptomatic PEs following laparoscopic cholecystectomy (RR, 0.48; 95% CI, 0.26-0.88; very low in the evidence of effects), but we are very uncertain of this finding. Given the very low baseline risk of VTE events in this specific patient population,[350] this would be expected to result in 0 fewer (0 fewer to 0 more) symptomatic PEs per 1000 patients. Similarly, pharmacological prophylaxis may not reduce symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects) or symptomatic distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; very low certainty in the evidence of effects). Again, given the very low baseline risks, this would correspond to 0 fewer (0 fewer to 0 more) events per 1000 patients for both outcomes. We are very uncertain about the effects on symptomatic proximal DVTs and symptomatic distal DVTs.

Harms and burden. Pharmacological prophylaxis may result in a small increase in major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This would be expected to result in 6 more (3 fewer to 20 more) major bleeds per 1000 patients. We are very uncertain whether pharmacological prophylaxis results in little or no difference in reoperation (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects); this corresponds to 1 fewer (8 fewer to 18 more) reoperation per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest

certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel based this recommendation on the trivial incremental benefits and the small increased risk of major bleeding associated with pharmacological prophylaxis. The panel judged that the potential benefits of pharmacological prophylaxis were outweighed by the small increased risk of major bleeding in average-risk patients undergoing laparoscopic cholecystectomy. This relates to the very low baseline risk of VTE for patients undergoing laparoscopic cholecystectomy. The panel discounted the mortality difference observed in this analysis as unlikely to relate to pharmacological prophylaxis, given the very low baseline risk of VTE. Patients with other risk factors for VTE (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Conclusions and research needs for this recommendation. The guideline panel determined that potential undesirable effects of pharmacological prophylaxis, in particular major bleeding, outweighed its potential benefit for patients undergoing laparoscopic cholecystectomy. The panel acknowledges that the overall certainty in the evidence was low, in particular as a result of indirectness, with most of the trial data included in the analysis involving patients undergoing major surgical procedures. Further research into pharmacological prophylaxis following laparoscopic cholecystectomy was not regarded as high priority given the low baseline incidence of VTE complications in this patient population.

Major neurosurgical procedures

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major neurosurgical procedures?

Recommendation 19

For patients undergoing major neurosurgical procedures, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remarks:** Patients undergoing major neurosurgical procedures are expected to receive prophylaxis with mechanical methods. Pharmacological prophylaxis may be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, pharmacological prophylaxis could be considered for patients undergoing major neurosurgical procedures that carried a lower risk for major bleeding and in those patients with persistent mobility restrictions after the bleeding risk declines following surgery.

Summary of the evidence. We identified 1 systematic review[358] that addressed this question. We identified 6 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[68,123,128,359-361] Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria.[135] We additionally searched for and identified 3 nonrandomized studies that informed this question.[362-364] All studies included patients undergoing neurosurgical procedures. Five studies assessed the effect of LMWH,[68,128,130,135,362] 4 studies assessed the effect of UFH,[359,361-363] 1 study assessed the effect of warfarin,[124] and 1 study assessed the effect of heparin-dihydroergotamine.[360] Additionally, across the 10 studies, mechanical prophylaxis was used as a cointervention in 6 of the randomized studies[68,123,128,130,135,359] and in all 3 of the nonrandomized studies.[361-363] Supplement 6 presents the characteristics of all included studies.

Five RCTs[68,104,128,130,359,362] and 2 nonrandomized studies[361,363] reported the effect of any pharmacological thromboprophylaxis vs no pharmacological intervention on mortality, 3 RCTs[123,128,360] and 2 nonrandomized studies reported on development of PEs,[361,363] 2 RCTs reported on screening-detected proximal DVTs,[128,130] and 1 study reported on development of screening-detected distal DVTs.[128] Seven RCTs[68,123,128,130,135,359,360] and 3 nonrandomized studies[361-363] reported risk of major bleeding, and 2 RCTs reported on risk of reoperation.[135,359]

The EtD framework is available online at https://guidelines.gradepro.org/profile/C5A1B92D-0E70-50BA-847C-0497617938F5.

Benefits. Pharmacological prophylaxis does not appear to reduce mortality (RR, 1.27; 95% CI, 0.57-2.69; low certainty in the evidence of effects) when considering the body of evidence from RCTs, in which we have more confidence than the nonrandomized data. This corresponds to 9 more deaths (15 fewer to 65 more) per 1000 patients. Based on RCT evidence, pharmacological prophylaxis may result in little or no difference in symptomatic PEs (RR, 0.84; 95% CI, 0.03-27.42; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 0 fewer events (2 fewer to 53 more) per 1000 patients based on a baseline risk of 0.2% from observational data.[364] The absolute effect size is similarly small when considering the body of evidence from nonrandomized trials. Pharmacological prophylaxis may result in a small, possibly unimportant, effect on symptomatic proximal DVTs (RR, 0.50; 95% CI, 0.30 to 0.84; low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 0.60; 95% CI, 0.33-1.08; very low certainty in the evidence of effects). This would correspond to 6 fewer (2-8 fewer) symptomatic proximal DVTs and 0 fewer (0-1 fewer) symptomatic distal DVTs per 1000 patients undergoing major neurosurgical procedures, based on baseline risks from observational data of 1.2% and 0.1%, respectively.[364]

Harms and burden. From RCTs, pharmacological prophylaxis may increase major bleeding (RR, 1.57; 95% CI, 0.70-3.50; low certainty in the evidence of effects), corresponding to 10 more (5 fewer to 43 more) events per 1000 patients undergoing major neurosurgical procedures. We are very uncertain of the effect of pharmacological prophylaxis on reoperation (RR, 0.43; 95% CI, 0.06-2.84; very low certainty in the evidence of effects), which would correspond to 18 fewer (29 fewer to 57 more) reoperations per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel noted that observed RR ratios from observational studies tended to view pharmacological prophylaxis more favorably than RCTs. The panel based its recommendation on RR ratios from meta-analysis of RCTs rather than observational studies, given the greater risk of bias with the latter studies. The panel noted that the small benefit of

pharmacological prophylaxis for the prevention of DVT was based upon randomized controlled studies using screening venography to detect rates of asymptomatic DVTs. The panel rated the harms of major bleeding associated with pharmacological prophylaxis as moderate because of the potential for greater morbidity associated with surgical site bleeding following these procedures. The panel recognized that patients undergoing major neurosurgical procedures would routinely receive prophylaxis with mechanical methods. The panel acknowledged that pharmacological prophylaxis might still be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, the panel acknowledged that pharmacological prophylaxis could be considered for patients undergoing neurosurgical procedures that carried a lower risk for major bleeding. It may also be considered for patients with persistent mobility restrictions after the bleeding risk subsides following surgery.

Conclusions and research needs for this recommendation. The panel judged, based on the available very low certainty evidence, that the expected net benefit favored no prophylaxis following major neurosurgical procures, because the potential small benefit of reducing VTE events was outweighed by the potential moderate increased risk of major bleeding. The panel also recognized that mechanical methods of thromboprophylaxis are commonly used in this patient population. There is a great need for the performance of large RCTs evaluating pharmacological prophylaxis following major neurosurgical procedures, and using clinically important end points, to add certainty to this recommendation. The panel acknowledges that the current recommendation may not reflect standard practice in some centers.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing major neurosurgical procedures?

Recommendation 20

For the subset of patients undergoing major neurosurgical procedures for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review[358] that addressed this question. We identified 4 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.[348,365-367] Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria.[368] All studies included patients undergoing neurosurgical procedures. Five studies reported the effect of LMWH compared with that of UFH on development of mortality,[348,365-368] 2 studies reported on the development of PEs,[365,366] 1 study reported on the development of screening-detected proximal DVTs,[348] and 1 study reported on screening-detected distal DVTs.[366] Four studies reported risk of major bleeding[348,365-367] and 1 study reported on risk of reoperation.[366]

All participants wore compression stockings, with the exception of 1 study in which their use was not reported.[368]

The EtD framework is available online at https://guidelines.gradepro.org/profile/E9D1EF22-EEC9-560E-A0CC-9FD435188BBE.

Benefits. Pharmacological prophylaxis with LMWH may result in little to no difference in mortality compared with UFH (RR, 0.34; 95% CI, 0.04-3.21; low certainty in the evidence of effects) following major neurosurgical procedures; this corresponds to 3 fewer (5 fewer to 11 more) deaths per 1000 patients. LMWH may result in little or no difference in symptomatic PEs (RR, 0.20; 95% CI, 0.01-4.03; low certainty in the evidence of effects) compared with UFH following major neurosurgical procedures. Based on a baseline risk of 0.2% from observational data,[364] this corresponds to 2 fewer (2 fewer to 6 more) symptomatic PEs in a cohort of 1000 patients following major neurosurgical procedures. We are uncertain whether LMWH affects proximal DVTs (RR, 1.00; 95% CI, 0.14-6.91; very low certainty in the evidence of effects). Similarly, the impact of LMWH on symptomatic distal DVTs is very uncertain (RR, 0.33; 95% CI, 0.01-7.93; very low certainty in the evidence of effects). In absolute terms, this corresponds to 1 fewer (1 fewer to 7 more) symptomatic distal DVT per 1000 patients, based on a baseline risk of 0.2% from observational data.[364]

Harms and burden. LMWH may result in little or no difference in major bleeding (RR, 0.76; 95% CI, 0.20-2.95; low certainty in the evidence of effects) compared with UFH, which corresponds to 5 fewer (18 fewer to 43 more) major bleeding events per 1000 patients. We were unable to assess the effect on reoperations.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. In formulating this recommendation, the panel formally acknowledges its prior conditional recommendation against pharmacological prophylaxis (Recommendation 19) for patients undergoing neurosurgical procedures. Nevertheless, if pharmacological prophylaxis is considered, the panel judged the desirable effects of LMWH over UFH as small and the undesirable effects as trivial. Considering the very low certainty in the evidence, and possibly important uncertainty about or variability in how much people value the main outcomes, the balance of effects favored LMWH. Equity, acceptability, and feasibility were not considered major factors.

Conclusions and research needs for this recommendation. In the subset of high-risk patients following major neurosurgical procedures for whom pharmacological prophylaxis is being considered, the ASH guideline panel judged the net benefit to favor LMWH over UFH. The panel recognizes this as being based upon very low certainty in the evidence.

The research priorities following major neurosurgical procedures are to better establish the benefits and risks of any pharmacological prophylaxis compared with no pharmacological prophylaxis. For patients considered at very high risk of postoperative VTE and at low bleeding risk, high-quality comparative studies of LMWH vs UFH using clinically important outcome measures would be of value.

Urological procedures. *Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing TURP?*

Recommendation 21

For patients undergoing TURP, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients with other risk factors for VTE (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Summary of the evidence. We did not identify any systematic reviews of RCTs addressing this research question. Because of the paucity of studies related to TURP, data across all major general, urological, and gynecological surgical procedures were pooled, and TURP-specific baseline risk estimates were applied, where available. The evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological prophylaxis was comparable to that used to inform this question for patients undergoing laparoscopic cholecystectomy (see Recommendation 18). To determine the desirable and undesirable effects of prophylaxis in absolute terms, the baseline risks specific for TURP outcomes were drawn from a systematic review by Tikkinen et al[369] and from observational studies.[370-372]

The EtD framework is available online at https://guidelines.gradepro.org/profile/05201A35-BCDA-9EFA-98CB-892C0AB72944.

Benefits. Pharmacological prophylaxis may not reduce overall mortality compared with no pharmacological prophylaxis (RR, 0.75; 95% CI, 0.61 to 0.93; low certainty in the evidence of effects). This corresponds to 1 fewer (0-1 fewer) death per 1000 patients undergoing TURP. Pharmacological prophylaxis may not reduce symptomatic PEs (RR, 0.48; 95% CI, 0.26 to 0.88; low certainty in the evidence of effects), which corresponds to 0 fewer events in lower-risk patients and 0 fewer (0-1 fewer) events in higher-risk patients undergoing TURP. We are very uncertain of its effect on symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), which would correspond to 1 fewer (0-1 fewer) symptomatic event in 1000 lower-risk patients or 3 fewer (0-5 fewer) events per 1000 higher-risk patients. We are very uncertain about its effect on symptomatic distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; very low certainty in the evidence of effects). Based upon the very low baseline risk for patients undergoing TURP, this would correspond to 0 fewer symptomatic events per 1000 higher-risk patients.

Harms and burden. The risk of major bleeding is probably slightly increased (RR, 1.24; 95% CI, 0.87-1.77; moderate certainty in the evidence of effects) with the use of pharmacological prophylaxis. This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients. We are very uncertain about reoperations (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects) related to pharmacological prophylaxis.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel judged the desirable effects of pharmacological prophylaxis for patients undergoing TURP as trivial and the undesirable effects as small in magnitude. It further judged that there was possibly important uncertainty or variability in how much people value the main outcomes. Based primarily on the very low baseline risk of VTE following TURP, the panel judged that the balance of effects ultimately favored not using pharmacological prophylaxis. Pharmacological prophylaxis would also incur moderate costs and not be cost-effective.

Conclusions and research needs for this recommendation. The guideline panel suggests against pharmacological prophylaxis for patients undergoing TURP. Based on overall very low certainty in the evidence, the panel judged that the desirable effects of pharmacological prophylaxis were outweighed by the undesirable effects, specifically the increased risk of bleeding in this setting. Given the very low baseline risks of VTE following this procedure and the increasing use of alternative modalities to treat lower urinary tract symptoms attributed to benign prostatic hyperplasia,[373] further RCTs conducted on patients undergoing TURP do not appear to be a major priority.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing TURP?

Recommendation 22

For the subset of patients undergoing TURP for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We did not identify any systematic reviews of RCTs addressing this research question. Because of the paucity of studies related to TURP, data across all major general, urological, and gynecological surgical procedures were pooled. Thirty-one studies reported the effect of LMWH vs UFH on risk of mortality,[305,307,308,310-312,314,317-319,321,322,325-327,329-339,341,342,346,347,374] and 36 studies reported on development of symptomatic PEs.[295,305-307,310-312,314-319,321,322,324,326-335,337,339,344-346,374-378] Six studies reported the effect of LMWH vs UFH on development of symptomatic proximal DVTs,[306,316,326,334,336,375] 8 studies reported the effect on development of symptomatic distal DVTs,[306,316,326,329,334,336,341,375] 31 studies reported on risk of major bleeding,[295,305-307,311,313,315-319,321-339,341,344-346,374-377,379] and 19 studies reported on risk of reoperation.[305,307,309,317,319,322,323,326,329,330,333-337,341,375-377] To determine the desirable and undesirable effects of prophylaxis in absolute terms, the baseline risks specific for TURP outcomes obtained from a systematic review by Tikkinen et al[369] were applied to the corresponding pooled RRs.

The EtD framework is available online at https://guidelines.gradepro.org/profile/59BDE78B-362E-9573-980D-41A280D79D9E.

Benefits. The risks of mortality may be similar for patients treated with LMWH and UFH (RR, 1.03; 95% CI, 0.89-1.18; very low certainty in the evidence of effects), but we are very uncertain of this finding. Given an assumed baseline risk of 0.2%,[370-372] this corresponds to 0 fewer (0 fewer to 0 more) deaths per 1000 patients. Similarly, there may be little difference for other outcomes,

such as symptomatic PEs (RR, 0.84; 95% CI, 0.59-1.20; very low certainty in the evidence of effects), corresponding to 0 fewer (0 fewer to 0 more) events per 1000 patients. We are equally uncertain about the risk of symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.0; very low certainty in the evidence of effects) and symptomatic severe distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects). Corresponding absolute effect size estimates are very small.

Harms and burden. The risks of bleeding may be similar with LMWH and UFH (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects), corresponding to 0 fewer (4 fewer to 3 more) major bleeding events per 1000 patients undergoing TURP. The use of LMWH does not appear to decrease the risk of reoperation (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the evidence of effects) for patients undergoing TURP. When applying a TURP-specific baseline risk of 0.2%, this corresponded to 0 fewer (0-1 fewer) reoperations per 1000 patients undergoing TURP.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel rated the magnitude of the desirable effects and undesirable effects of using LMWH or UFH as trivial. They further determined that there was possibly important uncertainty and/or variability in how much patients value the main outcomes. Overall, the balance of effects did not favor LMWH or UFH, nor did cost-effectiveness or issues surrounding equity, acceptability, and feasibility, at least for inpatient prophylaxis. The panel recognized that this particular comparison applied only to patients undergoing TURP considered at very high risk for VTE (eg, patients with a history of VTE) in whom pharmacological prophylaxis might be considered.

Conclusions and research needs for this recommendation. Based on very low certainty in the evidence for effects, the guideline panel did not find a net benefit for using LMWH or UFH for patients undergoing TURP in whom pharmacological prophylaxis is indicated and suggests that either can be used. For most patients undergoing TURP, the panel recommended against the use of pharmacological prophylaxis (see Recommendation 21). No high-priority research needs were identified.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing radical prostatectomy?

Recommendation 23

For patients undergoing radical prostatectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis.

Summary of the evidence. Because of the paucity of RCTs specific to this setting, the evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 21); we pooled data across all surgical procedures and applied surgery-specific baseline risk estimates for radical prostatectomy drawn from a systematic review by Tikkinen et al.[380]

The EtD framework is available online at https://guidelines.gradepro.org/profile/F99386B2-4C08-3F36-8029-61B51278B574.

Benefits. Pharmacological prophylaxis vs no prophylaxis may not reduce mortality (RR, 0.75; 95% CI, 0.61 to 0.93; low certainty in the evidence of effects), corresponding to 0 fewer deaths per 1000 patients. Pharmacological prophylaxis probably does not reduce symptomatic PEs (RR, 0.48; 95% CI, 0.26-0.88; moderate certainty in the evidence of effects). Depending on patient risk, this corresponds to 0 fewer symptomatic PEs in lower-risk patients to 0 fewer (0-1 fewer) symptomatic PEs per 1000 higher-risk patients undergoing radical prostatectomy. We are very uncertain about the effect on symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects). This corresponds to 1 fewer (0-1 fewer) symptomatic proximal DVT per 1000 lower-risk patients to 4 fewer (0-5 fewer) per 1000 higher-risk patients. Distal DVTs may be reduced (RR, 0.52; 95% CI, 0.31-0.87; low certainty in the evidence of effects), but this also corresponds to a negligible effect of 0 fewer symptomatic distal DVT events, irrespective of baseline risk category.

Harms and burden. Pharmacological prophylaxis compared with no prophylaxis may increase major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients undergoing radical prostatectomy. We are uncertain about the effect of pharmacological prophylaxis compared with no prophylaxis on reoperations (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects); this corresponds to 0 fewer (3 fewer to 6 more) reoperations per 1000 men based on a baseline risk of 0.4%.[380]

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel recognized during its deliberations that the practice of radical prostatectomy varies greatly, ranging from robotically assisted laparoscopic radical prostatectomy with no or a limited pelvic lymph node dissection to open radical prostatectomy with extended pelvic lymph node dissection. Based on a systematic review by Tikkinen et al,[380] this results in substantially different baseline risks for VTEs, which are important considerations for these recommendations. The majority of radical prostatectomies performed by urologists in the United States are performed robotically, typically with no or only a limited lymph node dissection. In this group, the panel judged the desirable effects of pharmacological prophylaxis as trivial and undesirable effects as small. Patients undergoing open radical prostatectomy with lymph node dissection were considered at higher risk for VTEs and bleeding. Cost-effectiveness probably favored no pharmacological prophylaxis, whereas issues of equity, acceptability, and feasibility were not deemed important in this setting.

Conclusions and research needs for this recommendation. The guideline panel judged that the net benefit favors no pharmacological prophylaxis for patients undergoing radical prostatectomy, based on very low certainty in the evidence of effects. The panel perceived it as important to emphasize that this recommendation was based on the panel's assessment of average patients undergoing radical prostatectomy in the form of robotically assisted laparoscopic prostatectomy with no or limited lymph node dissection. Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis. Further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to these recommendations. Further studies on patient values regarding prevention of VTEs and bleeding would allow for optimal shared decision making regarding thromboprophylaxis for radical prostatectomy.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing radical prostatectomy?

Recommendation 24

For patients undergoing radical prostatectomy in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using either LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects, (⊕◯◯◯).

Summary of the evidence. In the absence of RCTs specific to this setting, the evidence base to inform the relative effectiveness of LMWH prophylaxis vs UFH prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 22); we pooled data across all surgical procedures and applied surgery-specific baseline risk estimates for radical prostatectomy drawn from a systematic review by Tikkinen et al.[380]

The EtD framework is available online at https://guidelines.gradepro.org/profile/AEF71CF4-AB9F-1DDF-A08B-1F5E2484EA5F.

Benefits. The risks of mortality may be similar for patients treated with LMWH and UFH (RR, 1.03; 95% CI, 0.89-1.18; low certainty in the evidence of effects); this corresponds to 0 fewer deaths per 1000 men. Similarly, there may be little difference for the other outcomes of symptomatic PEs (RR, 0.84; 95% CI, 0.59-1.20; very low certainty in the evidence of effects), symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.0; very low certainty in the evidence of effects), and symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects), with all 95% CIs crossing the line of no effect and very small absolute effect sizes.

Harms and burden. The risks of bleeding may be similar with LMWH and UFH (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects), corresponding to 0 fewer (4 fewer to 3 more) major bleeding events per 1000 patients undergoing radical prostatectomy. The risks of reoperation may be similar with LMWH and UFH (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the evidence of effects), corresponding to 1 fewer (0-2 fewer) event based on a baseline risk of 0.4%.[380]

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel rated the magnitude of the desirable and undesirable effects of using LMWH over UFH as trivial. They further determined that there was possibly important uncertainty and/or variability in how much people value the main outcomes. Overall, the balance of effects did not favor LMWH or UFH, nor did cost-effectiveness or issues surrounding equity, acceptability, and feasibility, at least for inpatient prophylaxis. The panel recognized that this particular comparison applied only to select patients undergoing radical prostatectomy considered at high risk for VTEs (eg, patients with prior VTEs). For most patients undergoing radical prostatectomy, the panel recommended against the use of pharmacological prophylaxis (see Recommendation 23).

Conclusions and research needs for this recommendation. The guideline panel judged that, for patients undergoing radical prostatectomy requiring pharmacological prophylaxis, based upon very low certainty in the evidence, LMWH or UFH can be used. There is a need for high-quality randomized trials specific to patients undergoing radical prostatectomy, particularly those treated with robotically assisted laparoscopic prostatectomy, the most widely used surgical approach for clinically localized prostate cancer.

Cardiac or major vascular surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing cardiac or major vascular surgery?

Recommendation 25

For patients undergoing cardiac or major vascular surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis or no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. Our systematic search for RCTs identified 3 studies[70,381,382] that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the paucity of RCTs, we also systematically searched for observational studies and identified 1 additional study that fulfilled our inclusion criteria.[383]

One trial reported the effect of pharmacological prophylaxis vs no intervention on risk of mortality.[381] Two trials reported the effect on the risk of symptomatic PEs and on the risk of any proximal and distal DVTs.[70,381,382] The effect on the risk of major bleeding was reported from an RCT[381] and a nonrandomized controlled study.[383] Surgery-specific baseline risk estimates were obtained from a systematic review and meta-analysis of risk of VTE after cardiac surgery.[384]

The EtD framework is available online at https://guidelines.gradepro.org/profile/D5319730-F947-FFB7-B1F7-D4E9E4697079.

Benefits. We were unable to assess the effect of pharmacological prophylaxis on mortality (RR, not estimable because no deaths were observed, low certainty in the evidence of effects). Pharmacological prophylaxis appears to result in little or no difference in symptomatic PEs (RR, 2.40; 95% CI, 0.10-55.7; low certainty in the evidence of effects); this corresponds to 5 more (3 fewer to 198 more) PEs per 1000 patients receiving pharmacological prophylaxis based on a baseline risk of 0.4%.[384] We are very uncertain whether pharmacological prophylaxis results in little or no difference in proximal DVTs (RR, 2.85; 95% CI, 0.12-67.83; low certainty in the evidence of effects). This finding corresponds to 45 more (21 fewer to 1631 more) symptomatic proximal DVTs per 1000 patients, based on a baseline risk of 2.4%.[384] We are also very uncertain about the effect of pharmacological prophylaxis on distal DVTs (RR, 0.32; 95% CI, 0.01-7.54; very low certainty in the evidence of effects). This corresponds to 1 fewer (2 fewer to 13 more) symptomatic distal DVT per 1000 high-risk patients, based on a baseline risk of 0.2%.[384]

Harms and burdens. Based on 1 large observational study[383] and supported by a single relevant RCT,[381] the rates of major bleeding may be increased with pharmacological prophylaxis (RR, 1.26; 95% CI, 1.07-1.47; low certainty in the evidence of effects). This corresponds to 4 more (1-6 more) major bleeds per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes informed by observational studies.

Other EtD criteria and considerations. The panel recognized that very high doses of UFH are routinely administered to most patients undergoing cardiac and major vascular surgery. Thus, for this recommendation, the benefits and harms of postoperative pharmacological prophylaxis are being considered in an incremental context. The panel recognized there was a paucity of high-quality evidence addressing this particular question, and this recommendation was made in the face of very uncertain evidence. Based upon available evidence, the panel judged that the incremental desirable and undesirable effects of pharmacological prophylaxis were trivial and, therefore, balanced.

The panel recognized that cardiac surgery itself is associated with a risk for the development of heparin-induced thrombocytopenia (HIT). The panel reviewed the available literature and found that the risk of HIT among heparin preparations was higher with the use of UFH than with LMWH. Available evidence from RCTs did not allow the panel to quantitate whether there was an incremental risk for HIT associated with the use of pharmacological heparin prophylaxis beyond that of UFH administered during the procedure itself. However, the panel acknowledged that concerns about HIT would lead some panelists to be less likely to routinely use postoperative pharmacological prophylaxis with a heparin preparation, particularly UFH. The panel did not believe that there were important implementation considerations with the use of postoperative pharmacological prophylaxis in this patient population. Should LMWH or UFH be given, the panel recommended periodic monitoring of platelet counts because of the concern for postoperative HIT.

Conclusions and research needs for this recommendation. The panel found that the overall net benefit did not favor pharmacological prophylaxis or no pharmacological prophylaxis for patients undergoing cardiac and major vascular surgery; this was based on very low certainty in the evidence. For subgroup considerations, the panel judged that, for patients at higher baseline risk for VTE (eg, those with a history of VTE), pharmacological prophylaxis might be considered over no prophylaxis.

The panel supported that further research, in the form of well-designed RCTs using clinically important end points, is needed to determine the role of pharmacological prophylaxis in the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population is also warranted.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing cardiac or major vascular surgery?

Recommendation 26

When pharmacological prophylaxis is used for patients undergoing cardiac or major vascular surgery, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review[385] of RCTs and observational studies that addressed this research question. We identified 3 studies[386-388] in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our update of the systematic review did not identify any additional studies that fulfilled the inclusion criteria. One study reported the effect of LMWH vs UFH on the risk of mortality, PE, and major bleeding.[387] Three studies reported the effect of LMWH vs UFH on the risk of any DVT, including 1 study reporting data for proximal and distal DVTs separately.[386-398]

Surgery-specific baseline risk estimates were obtained from a systematic review and meta-analysis of risk of VTEs after cardiac surgery.[384]

The EtD framework is available online at https://guidelines.gradepro.org/profile/D32EF371-AE1E-1ACF-82CD-E11528E7B8E0.

Benefits. We are very uncertain whether LMWH vs UFH affects mortality following cardiac or major vascular surgery (RR, 4.55; 95% CI, 0.22-93.81; low certainty in the evidence of effects). This corresponds to 0 fewer deaths per 1000 patients. We were unable to estimate an effect on symptomatic PEs (RR, not estimable). We are also very uncertain about the effect of LMWH on symptomatic proximal DVTs (RR, 1.33; 95% CI, 0.30-6.01; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 1.20; 95% CI, 0.45-3.22; very low certainty in the evidence of effects). This would correspond to 8 more (17 fewer to 122 more) symptomatic proximal DVTs per 1000 patients and 0 more (1 fewer to 4 more) symptomatic distal DVTs per 1000 patients based on baseline risks of 2.4% and 0.2%, respectively.

Harms and burden. LMWH vs UFH appears to result in little or no difference in major bleeding (RR, 0.91; 95% CI, 0.19-4.42; low certainty in the evidence of effects). We found no data on reoperation.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for indirectness and very serious imprecision.

Other EtD criteria and considerations. The panel recognizes that they have judged that evidence was insufficient and of

very low quality to recommend for or against pharmacological prophylaxis following cardiac surgery. Nevertheless, particularly for patients considered at high risk for VTE (eg, those with history of VTEs), postoperative pharmacological prophylaxis would be considered for use in the cardiac and major vascular surgery settings by some panelists. This recommendation is relevant for patients considered at high risk for VTEs.

As discussed in the previous recommendation, HIT is a recognized complication in the cardiac and vascular surgery settings. Furthermore, it is recognized that the risk of HIT in other settings has been shown to be higher with the use of UFH vs LMWH. Available evidence from RCTs did not allow the panel to quantitate whether there was an incremental risk for HIT associated with the use of pharmacological UFH or LMWH prophylaxis beyond that of heparin administered during the procedure itself or whether there was a relatively greater incremental risk for HIT in the cardiac surgery setting with postoperative UFH prophylaxis than with LMWH. Nevertheless, given the above factors, if pharmacological prophylaxis is chosen for use, panelists concurred that an anticoagulant with a lower risk for HIT (eg, LMWH over UFH) should be considered.

The panel did not believe that there were important implementation considerations with use of postoperative LMWH or UFH pharmacological prophylaxis in this patient population. Should either agent be given, the panel recommended the periodic monitoring of platelet counts.

Conclusions and research needs for this recommendation. The panel judged that, based upon available evidence, LMWH or UFH could be selected for VTE prophylaxis following cardiac surgery based on very low quality evidence. The panel judged that this question was only of relevance for patients considered at very high risk for postoperative VTEs following cardiac or major vascular surgery in whom pharmacological prophylaxis would be considered over no prophylaxis.

The panel supported that the more important research question for this patient population is the role of pharmacological prophylaxis vs no pharmacological prophylaxis for the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population would also be of value.

Major trauma

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients experiencing major trauma?

Recommendation 27a

For patients experiencing major trauma at low to moderate risk for bleeding, the ASH guideline panel *suggests* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 27b

For patients experiencing major trauma at high risk for bleeding, the ASH guideline panel *suggests against* pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review that addressed this question.[389] We identified 2 studies[47,390] in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our update of the systematic review did not identify any additional studies that fulfilled the inclusion criteria. Two small studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of mortality, on development of symptomatic PEs, and on any DVT.[47,390] No study reported the effect of pharmacological prophylaxis compared with no intervention on risk of major bleeding or on risk of reoperation. The small amount of direct evidence, with a lack of information on undesirable outcomes, together with the very low certainty on the treatment effect, led the panel to consider the indirect data from hip fracture repair studies for treatment RR estimates[255-266] and applying baseline VTE and bleeding risks from studies on trauma patients.[391,392]

The EtD framework is available online at https://guidelines.gradepro.org/profile/434A9C2D-3417-F3ED-B7C1-4A0BA3EC6699.

Benefits. We are uncertain about the effect of pharmacological prophylaxis on mortality following major trauma (RR, 0.95; 95% CI, 0.84-1.07; very low certainty in the evidence of effects). Pharmacological prophylaxis may reduce symptomatic PEs, but we are very uncertain of this finding (RR, 0.49; 95% CI, 0.33-0.72; very low certainty in the evidence of effects). Depending upon baseline risk, this benefit corresponds to 3 fewer (2-5 fewer) patients with symptomatic PEs per 1000 moderate-risk patients and 2 fewer (1-2 fewer) patients per 1000 low-risk patients.

Pharmacological prophylaxis may also reduce the risk of proximal DVTs (RR, 0.51; 95% CI, 0.38-0.69; very low certainty in the evidence of effects), which corresponds to 7 fewer (4-9 fewer) in 1000 higher-risk patients and 3 fewer (2-4 fewer) in 1000 lower-risk patients. We are uncertain of the effect of pharmacological prophylaxis on distal DVTs (RR, 0.85; 95% CI, 0.5-1.29, very low certainty in the evidence of effects). This would correspond to 1 fewer (3 fewer to 2 more) symptomatic distal DVT in 1000 higher-risk patients and 0 fewer in 1000 lower-risk patients.

Harms and burden. Pharmacological prophylaxis may result in more major bleeding than no prophylaxis (RR, 1.24; 95% CI, 1.12-1.37; very low certainty in the evidence of effects), but this finding is uncertain. Depending upon baseline risk, the risk of major bleeding corresponds to 3 more (2-5 more) major bleeds per 1000 lower-bleeding-risk patients and to 14 more (7-21 more) major bleeds per 1000 patients with higher bleeding risk.

We are very uncertain about the effect of pharmacological prophylaxis on the need for reoperation (RR, 1.05; 95% CI, 0.82-1.35; very low certainty in the evidence of effects).

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The overall certainty in the evidence was rated as very low for this question, given the absence of RCTs comparing pharmacological prophylaxis vs no prophylaxis for patients experiencing major trauma. The benefits and harm/burden data were extrapolated from the closest surgical indication for which we had adequate comparative evidence (ie, hip fracture repair). It is recognized that these hip

fracture studies are dated and that rates of patient-important DVT events were derived from modeling of asymptomatic events detected by routine screening studies. The panel presumed that, in the absence of specific contraindications (eg, lower limb injuries), patients experiencing major trauma would receive mechanical prophylaxis. The panel emphasized the need to periodically reevaluate bleeding risk as patients recover from major trauma. Once bleeding is stabilized and the patient is no longer considered at high risk for major bleeding, the use of pharmacological prophylaxis should be reconsidered.

Conclusions and research needs for this recommendation. Based upon the totality of the evidence, the panel judged that the moderate overall benefits of pharmacological prophylaxis outweighed the increased risk of major bleeding for patients at low or moderate risk for bleeding. In contrast, for patients at high risk for major bleeding, the large undesirable consequences of major bleeding led to a balance that favors no pharmacological prophylaxis. The very low certainty in the evidence justifies conditional recommendations for both scenarios.

Well-designed trials using clinically important VTE end points are required for patients at low to moderate risk for bleeding following trauma to determine the incremental benefits of pharmacological prophylaxis beyond mechanical methods alone. Well-designed studies are also needed to determine the benefits and risks of introducing delayed pharmacological prophylaxis for patients experiencing major bleeding, including intracranial hemorrhage as a consequence of major trauma, as the bleeding risk subsides.

Question: Should LMWH vs UFH be used for patients experiencing major trauma?

Recommendation 28

For patients experiencing major trauma in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Summary of the evidence. We identified 1 systematic review that addressed this question.[389] Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria,[394] and our systematic search of RCTs identified 2 studies that fulfilled the inclusion criteria[394,395] and were not included in the review. Three studies reported the effect of LMWH prophylaxis vs UFH prophylaxis on risk of mortality, on development of any PEs, and on major bleeding,[393-395] whereas 2 studies informed on the risk of development of proximal and distal DVTs.[393,394]

The EtD framework is available online at https://guidelines.gradepro.org/profile/96D5A309-8606-4469-B732-E1844465CC75.

Benefits. LMWH vs UFH appears to result in little or no difference in mortality for patients experiencing major trauma (RR, 1.32; 95% CI, 0.14-12.39; low certainty in the evidence of effects). This corresponds to 2 more (4 fewer to 54 more) deaths per 1000 trauma patients receiving LMWH vs UFH. Similarly, LMWH may result in little or no difference in symptomatic PEs (RR, 1.04; 95% CI, 0.11-9.92; low certainty in the evidence of effects). This corresponds to 0 fewer (6 fewer to 61 more) symptomatic PEs per 1000 patients based on a baseline risk of 0.7% from observational data.[391] LMWH vs UFH likely results in no important effect on proximal DVTs (RR, 0.57; 95% CI, 0.25-1.31; moderate certainty in the evidence of effects). This corresponds to 3 fewer (5 fewer to 2 more) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 0.7% from observational data.[391]

LMWH probably also results in little or no difference in symptomatic distal DVTs (RR, 0.74; 95% CI, 0.46-1.20; moderate certainty in the evidence of effects). This corresponds to 0 fewer symptomatic distal DVTs per 1000 patients based on a baseline risk of 0.1% from observational data.[391]

Harms and burden. LMWH may result in a small increase in major bleeding (RR, 2.4; 95% CI, 0.53-10.78; low certainty in the evidence of effects). This corresponds to 20 more (7 fewer to 138 more) major bleeding events per 1000 patients receiving LMWH vs UFH. There were no comparative data about rates of reoperation of LMWH vs UFH following major trauma.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for very serious imprecision.

Other EtD criteria and considerations. The panel judged that the minor differences in the effects of the interventions on benefits and undesirable outcomes led to an overall balance that did not favor either intervention. The benefits observed with LMWH were limited to a minor reduction in the rates of symptomatic proximal DVTs, which was negated by the small observed increased risk of major bleeding. It was recognized that patients at high risk for major bleeding were excluded from the studies that formed the basis of this recommendation.

Because LMWH and UFH are in widespread use for this indication, the panel did not judge there to be major implementation considerations with either intervention. The panel presumed that, in the absence of specific contraindications (eg, lower limb injuries), patients experiencing major trauma would receive mechanical prophylaxis.

Conclusions and research needs for this recommendation. The panel suggested that, for patients experiencing major trauma who are judged to be at low to moderate risk for bleeding, LMWH or UFH may be used for pharmacological VTE prophylaxis based on low certainty in the evidence.

The panel judged that the research priorities in major trauma related to establishing the effectiveness and the timing of intervention with pharmacological prophylaxis for patients receiving mechanical prophylaxis following major trauma, rather than comparative studies of LMWH vs UFH.

Major gynecological surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major gynecological surgery?

Recommendation 29

For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.[29] We identified only 5 studies[118,273-275,349] in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the paucity of studies on patients undergoing major gynecological procedures, data across major general, laparoscopic cholecystectomy, and major gynecological and urological procedures were pooled. The evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological prophylaxis was comparable to that used to inform this question for patients undergoing laparoscopic cholecystectomy (see Recommendation 18). Baseline risk estimates specific to gynecological procedures[396,397] were applied to determine the desirable and undesirable effects of prophylaxis in absolute terms.

The EtD framework is available online at https://guidelines.gradepro.org/profile/B2FDFE66-5A79-4E46-875E-9BB7F3FAFF9F.

Benefits. Pharmacological prophylaxis probably reduces mortality slightly following major gynecological surgery (RR, 0.75; 95% CI, 0.61-0.93; low certainty in the evidence of effects). This corresponds to a benefit of 4 fewer (1-7 fewer) deaths per 1000 patients. Pharmacological prophylaxis probably reduces the risk of symptomatic PEs (RR, 0.48; 95% CI, 0.26-0.88; low certainty in the evidence of effects), corresponding to a benefit of 2 fewer (0-3 fewer) symptomatic PEs per 1000 higher-risk patients and 0 fewer (0-1 fewer) per 1000 lower-risk patients, based on baseline risks from observation data of 0.1% and 0.4%, respectively.[396,397]

We are uncertain whether pharmacological prophylaxis reduces the rates of proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), corresponding to reduction of 4 fewer (0-6 fewer) symptomatic proximal DVTs per 1000 lower-risk patients and 17 fewer (0-23 fewer) per 1000 higher-risk patients based on baseline risks from observation data of 0.7% and 2.7%, respectively.[396,397] We are uncertain about the effect of pharmacological prophylaxis on distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; low certainty in the evidence of effects), corresponding to no reduction per 1000 patients treated based on a lower baseline risk of 0.1%.

Harms and burden. Pharmacological prophylaxis may slightly increase the risk of major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients receiving pharmacological prophylaxis. Pharmacological prophylaxis does not appear to increase the risk of reoperation (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects) following major gynecological procedures.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel based its recommendation on the judgment that the desirable benefits of pharmacological prophylaxis outweighed the likely small increased risk of major bleeding following major gynecological procedures. The panel acknowledges that the overall certainty in the evidence was very low given the issue of indirectness, with most of the available trial data not being specific to gynecological procedures. The panel considered that patients at increased risk for VTE would receive mechanical prophylaxis in addition to pharmacological prophylaxis. There were no major implementation considerations.

Conclusions and research needs for this recommendation. The panel judged that pharmacological prophylaxis should be administered to patients undergoing major gynecological surgery, and this recommendation was conditional given the very low certainty in the evidence. There is a need for large high-quality clinical trials using clinically relevant end points to determine the benefit of pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.

Question: Should LMWH vs UFH prophylaxis be used for patients undergoing major gynecological surgery?

Recommendation 30

For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.[30] We identified only 4 studies[374,376,377,379] overall that were conducted with patients undergoing major gynecological surgery. Because of the paucity of studies on patients undergoing major gynecological procedures, data across major general, laparoscopic cholecystectomy, and major gynecological and urological procedures were pooled. The evidence base to inform the relative effectiveness of LMWH prophylaxis vs UFH prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 22).

Baseline risk estimates specific to gynecological procedures[396,397] were applied to determine the desirable and undesirable effects of prophylaxis in absolute terms.

The EtD framework is available online at https://guidelines.gradepro.org/profile/F213C6D1-F2D9-221A-B8EE-92B6F94F5BB3.

Benefits. LMWH prophylaxis appears to result in little or no difference in mortality compared with UFH prophylaxis (RR, 1.03; 95% CI, 0.89-1.18; low certainty in the evidence of effects), corresponding to 1 more (2 fewer to 3 more) deaths per 1000 patients. Likewise, use of LMWH prophylaxis vs UFH prophylaxis appears to result in little or no difference in symptomatic PEs (RR, 0.91; 95% CI, 0.63-1.3; low certainty in the evidence of effects). For a higher baseline risk of 0.4% from observational data,[396] this corresponds to 1 fewer (2 fewer to 1 more) symptomatic PE per 1000 participants. For symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.00; low certainty in the evidence of effects), the absolute risk reduction is 0 per 1000 patients, with the 95% CI varying by baseline risk from 5 fewer to 27 more[397] to 22 fewer to 108 more (baseline risks of 0.7% and 2.7%, respectively).[396] We are very uncertain about the effect on symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects) following major gynecological surgical procedures.

Harms and burden. LMWH appears to confer little or no difference in major bleeding compared with UFH prophylaxis following major gynecological procedures (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects); this corresponds to 0 fewer (4 fewer to 3 more) major bleeds per 1000 patients. LMWH prophylaxis may result in a small, possibly unimportant, reduction in reoperations compared with UFH (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the evidence of effects). This corresponds to 4 fewer (8 fewer to 1 more) reoperation procedures per 1000 patients receiving LMWH prophylaxis.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and indirectness.

Other EtD considerations. The panel based its recommendation on the judgment that the desirable benefits and the risk of complications were balanced between use of LMWH and UFH pharmacological prophylaxis. The panel acknowledges that the overall certainty in the evidence was very low, given the issue of indirectness, with most of the available trial data not being specific to gynecological procedures. There was not deemed to be any major implementation consideration.

Conclusions and research needs for this recommendation. The panel suggests using LMWH or UFH for patients undergoing major gynecological surgery procedures based upon very low certainty in the evidence of effects. There is a need for large high-quality clinical trials using clinically relevant end points to determine the relative benefits of LMWH vs UFH pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.

Limitations of these guidelines

The panel recognized that many studies of pharmacological and mechanical prophylaxis for VTE prevention following major surgery date back decades, thereby raising questions about the applicability of this evidence. This includes largely outdated means (eg, venography) to assess for VTEs postoperatively. Surgical practice has changed considerably over the decades, aimed at improving the patient experience. In most circumstances, these innovations would be expected to reduce the overall risk of postoperative VTEs. Examples of such innovations include use of minimally invasive surgical procedures, early and increased postoperative patient mobilization, and use of regional anesthesia; however, it is uncertain whether such changes in surgical practice impact the relative effectiveness of various thromboembolic interventions. Therefore, for the purpose of this guideline, this type of evidence informing the relative effectiveness of these interventions was included when obtained in the setting of RCTs. For determining baseline risk of VTEs and major bleeding, we used data, where available, from contemporary large cohort studies that were deemed representative of contemporary patients.

Although the panel rated symptomatic VTE end points as those upon which recommendations should be based, the panel recognized that most studies of VTE prophylaxis following surgery used asymptomatic DVTs detected by the routine performance of sensitive screening tests (eg, venography) as the primary study outcome. Reporting of symptomatic DVTs in some studies could have been influenced by diagnostic suspicion bias. The panel also acknowledges that modeling was required to determine rates of symptomatic DVTs when only asymptomatic DVT events were reported, based on the best available estimates drawn from the literature.

The panel recognized that most of the evidence on mechanical methods of VTE prophylaxis comes from the orthopedic literature. Studies of the benefits of mechanical prophylaxis for other surgical settings are needed. Finally, the panel acknowledges that, for some questions, limited direct data were available (eg, VTE prophylaxis following urological and gynecological procedures and for major trauma). In these settings, estimates of the benefits of prophylaxis were based upon related surgical settings, such as general surgical procedures and hip fracture surgery, respectively.

What are others saying and what is new in these ASH guidelines?

These ASH guidelines stand out by their scope, which includes general issues relevant to any surgical procedure and those related to surgical subspecialties. They make consistent use of high-quality systematic reviews and provide a formal EtD framework for every recommendation, thereby enhancing transparency about the judgments that were made.

A widely used high-quality guideline is the 2012 Guideline of the American College of Chest Physicians (ACCP), which places a strong emphasis on patients' VTE risk scores.[398] In the guideline recommendations for VTE prevention in nonorthopedic surgical patients, patient-oriented VTE risk calculators, such as the Caprini score[10] and Rogers score,[399] were adopted. When the risk for VTE is very low, it was recommended not to use pharmacological or mechanical prophylaxis. For patients at low risk for VTE, mechanical prophylaxis was suggested over no prophylaxis, preferably with intermittent pneumatic compression. For patients at moderate risk for VTE who are not at high risk for major bleeding complications, it was suggested to use LMWH, low-dose UFH, or mechanical prophylaxis with intermittent pneumatic compression over no prophylaxis. For patients at high risk for VTE who are not at high risk for major bleeding complications, it was recommended to use pharmacological prophylaxis with LMWH or low-dose UFH over no prophylaxis, and it was suggested to add mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression to pharmacological prophylaxis. Guidelines by the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Clinical Excellence (NICE) also emphasize the importance of risk stratification.[400,401]

Mechanical methods of perioperative VTE prophylaxis have been addressed by a number of guidelines.[398,400-404] The 2012 ACCP guidelines did not provide a detailed comparison of the effectiveness of graduated compression stockings and pneumatic compression stockings, but they generally favor pneumatic compression stockings on the basis of indirect evidence, from the Clots in Legs or Stockings after Stroke trial for patients with stroke, that elastic stockings increased the risk of skin complications without reducing the risk of VTEs.[405] Other guidelines presented by SIGN,[400] NICE,[401] the American Academy of Orthopedic Surgeons (AAOS),[402] the Neurocritical Society,[404] and the International Union of Angiology[403] discuss the use of pneumatic compression and graduated compression stockings in various surgical settings but generally consider these modalities together as "mechanical devices" and do not offer a

direct comparison of their effectiveness or safety other than noting that graduated compression stockings cannot be used for patients with certain lower extremity pathologies.

Guidelines addressing the prophylactic placement of IVC filters include the 2012 ACCP guidelines,[398] the 2011 AAOS guideline for orthopedic patients,[402] the 2013 European Venous Forum,[403] the 2013 guidelines by the Neurocritical Care Society,[404] the 2013 British Committee for Standards in Hematology guidelines, and the "appropriateness criteria" by the American College of Radiology.[406] The recommendation made by these ASH guidelines corresponds with many of these existing recommendations that are mostly critical of prophylactic IVC filter placement for patients requiring major surgery or who have experienced trauma.

Several recent guidelines comment on VTE prophylaxis after total hip or knee arthroplasty. The 2012 ACCP guideline for orthopedic surgery patients[407] recommended LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose UFH, adjusted-dose vitamin K antagonists (VKAs), ASA, and/or intermittent pneumatic compression, with the proviso that they are portable, out of concerns regarding compliance. They further indicate a preference for LMWH over the other listed agents, with the exception of ASA. The 2011 AAOS guideline[402] recommends some form of chemoprophylaxis (including ASA) along with intermittent pneumatic compression after total hip or knee arthroplasty. The 2012 Asian Venous Thromboembolism Guideline[408] recommends LMWH, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran, warfarin, or ASA with intermittent pneumatic compression, referencing and effectively accepting the 2012 ACCP and 2011 AAOS guidelines. The 2013 International Angiology guideline favors LMWH, fondaparinux, VKAs, rivaroxaban, apixaban, or dabigatran, along with use of intermittent pneumatic compression after total hip arthroplasty.[403] The most current NICE guideline recommends LMWH or rivaroxaban after total hip arthroplasty and the same after total knee arthroplasty, with the additional option of ASA.[401]

For VTE prophylaxis after surgery for hip fractures, the 2012 ACCP guideline recommends LMWH for VTE prophylaxis vs fondaparinux and low-dose UFH over adjusted-dose VKAs or ASA.[407] Concurrent use of an intermittent pneumatic compression device was also recommended. The 2011 AAOS guideline does not specifically address hip fractures; however, in the face of hip arthroplasty as a treatment for hip fracture, their recommendations of some form of chemoprophylaxis (including ASA), along with intermittent pneumatic compression for total hip arthroplasty, would be applicable.[402] The 2012 Asian Venous Thromboembolism Guideline recommended LMWH, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran, warfarin, or ASA with intermittent pneumatic compression.[408] The Agency for Healthcare Research and Quality 2017 guideline favors chemoprophylaxis but is neutral on specific agents because of a lack of evidence.[236] The 2013 International Angiology Guideline favors LMWH, fondaparinux, VKAs, or low-dose UFH.[403] The most current NICE guideline recommends LMWH or fondaparinux.[401]

For general and abdominal surgery, which includes gastrointestinal, urological, gynecological, bariatric, vascular, plastic, or reconstructive surgery in its scope, the 2012 ACCP guidelines are once again the best known. In the very low risk setting, no specific pharmacological or mechanical prophylaxis is recommended other than early ambulation. At low risk, mechanical prophylaxis (preferably with intermittent pneumatic compression) is suggested over no prophylaxis. For moderate-risk patients, assuming there is no high risk for major bleeding, LMWH, low-dose UFH, and mechanical prophylaxis, preferably with intermittent pneumatic compression devices, are all options. If patients are at high risk for major bleeding complications or if consequences of bleeding are thought to be particularly severe, mechanical prophylaxis (preferably with intermittent pneumatic compression devices) is suggested over no prophylaxis.[398]

For patients undergoing neurosurgical procedures, there are a total of 6 guidelines that offer somewhat conflicting recommendations on pharmacological VTE prophylaxis. These guidelines include the 2012 ACCP guideline, the 2014 Korean Society of Thrombosis and Hemostasis Evidence-Based Clinical Practice Guidelines, the 2018 NICE guideline, the 2010 SIGN guideline, the 2017 European Society of Anesthesiology guideline, and the 2016 Neurocritical Care Society guidelines.[398,400,401,404,409,410] The recommendations provided by these current ASH guidelines are similar to the 2010 SIGN guidelines, the 2019 Congress of Neurological Surgeons Guidelines for Spine Trauma, and the 2012 ACCP guidelines. Overall, mechanical prophylaxis is recommended for most neurosurgical patients. The benefit of pharmacological prophylaxis should be considered for patients at high risk or very high risk for VTE, but the overall risk/benefit profile is questionable, given an increase in bleeding events, particularly because neurosurgical bleeding events can be more serious. Similar to the 2010 SIGN recommendations, our ASH guidelines suggest that, for patients who do receive pharmacological prophylaxis, LMWH be used over UFH, whereas the 2012 ACCP guidelines do not give preference to any specific drug.

Urology is covered within the scope of guidelines by the ACCP, the Australian National Health and Medical Research Council, and the National Institute for Health and Care Excellence, among others.[411] Urology-specific guidelines are available from the American Urological Association, the German Association of Scientific Medical Societies, and, most recently, the European Association of Urology.[412-414] In the absence of direct evidence for urology, the European Association of Urology guideline makes the assumption of a 50% risk reduction for "any serious VTE event" as well as a 50% increase in the risk of major bleeding requiring reoperation. When assessing the net benefit in making the recommendation, the major bleeding was given twice the weight of the outcome of VTE prevention. The resulting recommendations were supported by a systematic review of the procedure-specific VTE risk and the bleeding risk.[369,380] For patients undergoing TURP, this resulted in a conditional recommendation against pharmacological prophylaxis across risk groups. For radical prostatectomy, the guideline provides a more nuanced set of recommendations that differ by surgical approach (open, laparoscopic, or robotically assisted laparoscopic) and extent of the node dissection (without, standard, or extended). For patients undergoing robotically assisted laparoscopic prostatectomy with a standard lymph node dissection, which was considered the index case for these ASH guidelines, there is a conditional recommendation against pharmacological prophylaxis.

For cardiac surgery patients with an uncomplicated postoperative course, the 2012 ACCP guideline suggested the use of

mechanical prophylaxis, preferably with optimally applied intermittent pneumatic compression, over no prophylaxis or pharmacological prophylaxis.[398] For cardiac surgery patients whose hospital course is prolonged by ≥1 nonhemorrhagic surgical complication, the guideline suggested adding pharmacological prophylaxis with UFH or LMWH to mechanical prophylaxis. They considered that the risk of VTE following cardiac surgery is uncertain but judged that most patients were at moderate risk for VTEs and at high risk for anticoagulant prophylaxis-related bleeding. Based on these considerations, it was concluded that, in cardiac patients at usual risk for VTE, the harms of anticoagulant prophylaxis outweighed the benefits, whereas anticoagulation may be of net benefit for patients with high-risk characteristics. The ACCP guidelines did not provide recommendations specific to major vascular surgery. The International Consensus Statement on Prevention and Treatment of Venous Thromboembolism published by the European Venous Forum, in cooperation with several other organizations, offers guidelines for general, vascular, bariatric, and plastic surgical patients.[403] Major vascular surgery was considered with other "major surgery," and patients were judged to generally be at moderate risk in the absence of specific high-risk characteristics, such as age older than 60 years or prior VTE. Pharmacological prophylaxis was recommended in the absence of unusual bleeding risks. Recommendations specific to cardiac surgery patients were not presented. An update of NICE guidelines published in 2018 offers guidelines regarding VTE prophylaxis for patients undergoing cardiac or major vascular surgery.[401] This guideline recommends considering mechanical VTE prophylaxis on admission for patients who are undergoing cardiac surgery and are at increased risk for VTE and continuing this until the patient no longer has significantly reduced mobility relative to their normal or anticipated mobility. They recommend considering pharmacological VTE prophylaxis for a minimum of 7 days for patients who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, and whose risk of VTE outweighs their risk of bleeding. Further, they recommend considering mechanical prophylaxis on admission for people who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, if pharmacological prophylaxis is contraindicated. SIGN published a relevant updated guideline in 2014.[400] The guideline notes that cardiac surgery patients often receive anticoagulants and antiplatelet agents for reasons independent of VTE and that this may impact their VTE risk. Despite this, these guidelines recommend that patients undergoing coronary artery bypass grafting surgery should be offered mechanical thromboprophylaxis where feasible and that patients undergoing coronary artery bypass grafting surgery who are not at high risk for bleeding can also be offered pharmacological thromboprophylaxis.

The most relevant guideline on the perioperative management of trauma patients is that by the ACCP in 2012.[398] For major trauma, including traumatic brain injury, acute spinal injury, and traumatic spine injury, VTE prophylaxis is suggested (over no prophylaxis) with LMWH, low-dose UFH, or mechanical prophylaxis, preferably with intermittent pneumatic compression. For patients at high risk for VTE, addition of mechanical prophylaxis to pharmacological prophylaxis is suggested when not contraindicated by lower extremity injury. It further suggests against placement of an IVC filter for primary VTE prevention, as well as against periodic surveillance with venous compression ultrasound.

A guidance document from the American College of Gynecology dates back to 2007[415]; as a result, the 2012 ACCP guidelines provide the timeliest guidance for gynecological surgery. One set of recommendations is made across gastrointestinal, urological, gynecological, bariatric, vascular, plastic, and reconstructive surgery (see above).

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD framework.[416] The Agency for Healthcare Research and Quality in the United States provides a guide for implementing effective quality improvement in this patient population.[417]

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Authorship

Contribution: D.R.A. and P.D. wrote the first draft of the manuscript and revised the manuscript based on the authors' suggestions; C.B., F.D., C.W.F., D.A.G., S.R.K., M.R., A.R., F.B.R., M.A.S., K.A.O.T., and A.J.Y. critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (G.P.M., T.B., S.B., J.L.B., I.E.-I., H.J., I.N., W.W., J.J.Y.-N., and H.J.S.) contributed evidence summaries to the guidelines; D.R.A. and P.D. were the chair and vice chair of the panel and led the panel meeting; and all authors approved the content.

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References

1. Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ*. 2014;186(3):E123-E142.
2. Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
3. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
4. Schünemann HJ, Al-Ansary LA, Forland F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548-553.
5. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
6. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011; 64(4):383-394.
7. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. *Arch Intern Med*. 2003;163(14):1711-1717.
8. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med*. 2002;162(11):1245-1248.
9. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost*. 2003;90(3):446-455.
10. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*. 2005;51(2-3):70-78.
11. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med*. 1998;158(14):1525-1531.
12. Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016;353:i2089.
13. Alonso-Coello P, Schünemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016.
14. Atkins D, Eccles M, Flottorp S, et al; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4(1):38.
15. Schünemann HJ, Best D, Vist G, Oxman AD; GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *CMAJ*. 2003;169(7):677-680.
16. Schünemann HJ, Mustafa R, Brozek J, et al; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.
17. Lo B, Field MJ. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: The National Academies Press; 2009.
18. Akl EA, El-Hachem P, Abou-Haidar H, Neumann I, Schünemann HJ, Guyatt GH. Considering intellectual, in addition to financial, conflicts of interest proved important in a clinical practice guideline: a descriptive study. *J Clin Epidemiol*. 2014;67(11):1222-1228.
19. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med*. 2010;152(11):738-741.
20. Schünemann HJ, Osborne M, Moss J, et al; ATS Ethics and Conflict of Interest Committee and the Documents Development and Implementation Committee. An official American Thoracic Society policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med*. 2009;180(6):564-580.
21. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4): 395-400.
22. Marker States Database (software). McMaster University (developed by Evidence Prime, Inc.). Available at https://ms.gradepro.org/. Accessed 9 September 2019.
23. Eppsteiner RW, Shin JJ, Johnson J, van Dam RM. Mechanical compression versus subcutaneous heparin therapy in postoperative and posttrauma patients: a systematic review and meta-analysis. *World J Surg*. 2010;34(1):10-19.
24. Feng JP, Xiong YT, Fan ZQ, Yan LJ, Wang JY, Gu ZJ. Efficacy of intermittent pneumatic compression for venous thromboembolism prophylaxis in patients undergoing gynecologic surgery: A systematic review and meta-analysis. *Oncotarget*. 2017;8(12):20371-20379.
25. Ho KM, Tan JA. Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation*. 2013;128(9):1003-1020.
26. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev*. 2016;9:CD005258.
27. Morris RJ, Woodcock JP. Intermittent pneumatic compression or graduated compression stockings for deep vein thrombosis prophylaxis? A systematic review of direct clinical comparisons. *Ann Surg*. 2010;251(3):393-396.
28. O'Connell S, Bashar K, Broderick BJ, et al. The use of intermittent pneumatic compression in orthopedic and neurosurgical postoperative patients: a systematic review and meta-analysis. *Ann Surg*. 2016;263(5):888-889.

29. Pavon JM, Adam SS, Razouki ZA, et al. Effectiveness of Intermittent pneumatic compression devices for venous thromboembolism prophylaxis in high-risk surgical patients: a systematic review. *J Arthroplasty*. 2016;31(2):524-532.

30. Rahn DD, Mamik MM, Sanses TV, et al; Society of Gynecologic Surgeons Systematic Review Group. Venous thromboembolism prophylaxis in gynecologic surgery: a systematic review. *Obstet Gynecol*. 2011;118(5):1111-1125.

31. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2014; (12):CD001484.

32. Sobieraj DM, Coleman CI, Tongbram V, et al. Comparative effectiveness of combined pharmacologic and mechanical thromboprophylaxis versus either method alone in major orthopedic surgery: a systematic review and meta-analysis. *Pharmacotherapy*. 2013;33(3):275-283.

33. Zareba P, Wu C, Agzarian J, Rodriguez D, Kearon C. Meta-analysis of randomized trials comparing combined compression and anticoagulation with either modality alone for prevention of venous thromboembolism after surgery. *Br J Surg*. 2014;101(9):1053-1062.

34. Blanchard J, Meuwly JY, Leyvraz PF, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br*. 1999;81(4): 654-659.

35. Camporese G, Bernardi E, Prandoni P, et al; KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. *Ann Intern Med*. 2008;149(2):73-82.

36. Celebi F, Balik AA, Yildirgan MI, Başoğlu M, Adigüzel H, Oren D. Thromboembolic prophylaxis after major abdominal surgery [in Turkish]. *Ulus Travma Derg*. 2001;7(1):44-48.

37. Chin PL, Amin MS, Yang KY, Yeo SJ, Lo NN. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial. *J Orthop Surg (Hong Kong)*. 2009;17(1):1-5.

38. Coe NP, Collins RE, Klein LA, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. *Surgery*. 1978;83(2):230-234.

39. Colwell CW Jr, Froimson MI, Mont MA, et al. Thrombosis prevention after total hip arthroplasty: a prospective, randomized trial comparing a mobile compression device with low-molecular-weight heparin. *J Bone Joint Surg Am*. 2010;92(3):527-535.

40. Fasting H, Andersen K, Kraemmer Nielsen H, et al. Prevention of postoperative deep venous thrombosis. Low-dose heparin versus graded pressure stockings. *Acta Chir Scand*. 1985;151(3):245-248.

41. Francis CW, Pellegrini VD Jr, Marder VJ, et al. Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA*. 1992;267(21):2911-2915.

42. Ginzburg E, Cohn SM, Lopez J, Jackowski J, Brown M, Hameed SM; Miami Deep Vein Thrombosis Study Group. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg*. 2003;90(11):1338-1344.

43. Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am*. 1990;72(1):27-31.

44. Heiss-Dunlop W, Hamer H, Pitto R. Safety and efficacy of pneumatic compression with foot-pumps for prophylaxis against deep vein thrombosis after total hip joint replacement. A randomized clinical trial. *J Bone Joint Surg Br*. 2018(87B):suppl 1.

45. Kaempffe FA, Lifeso RM, Meinking C. Intermittent pneumatic compression versus coumadin. Prevention of deep vein thrombosis in lower-extremity total joint arthroplasty. *Clin Orthop Relat Res*. 1991; (269):89-97.

46. Knudson MM, Collins JA, Goodman SB, McCrory DW. Thromboembolism following multiple trauma. *J Trauma*. 1992;32(1):2-11.

47. Knudson MM, Lewis FR, Clinton A, Atkinson K, Megerman J. Prevention of venous thromboembolism in trauma patients. *J Trauma*. 1994;37(3):480-487.

48. Knudson MM, Morabito D, Paiement GD, Shackleford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma*. 1996;41(3):446-459.

49. Kosir MA, Kozol RA, Perales A, et al. Is DVT prophylaxis overemphasized? A randomized prospective study. *J Surg Res*. 1996;60(2):289-292.

50. Kosir MA, Schmittinger L, Barno-Winarski L, et al. Prospective double-arm study of fibrinolysis in surgical patients. *J Surg Res*. 1998;74(1):96-101.

51. Kurtoglu M, Yanar H, Bilsel Y, et al. Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg*. 2004;28(8):807-811.

52. Macouillard G, Castagnera L, Claverie JP, et al. Prevention of deep venous thrombosis in spinal surgery: comparison of intermittent sequential pneumatic compression versus low molecular weight heparin. *Thromb Haemost*. 1993;69:646.

53. McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *BMJ*. 1980;280(6213):514-517.

54. Mellbring G, Palmér K. Prophylaxis of deep vein thrombosis after major abdominal surgery. Comparison between dihydroergotamine-heparin and intermittent pneumatic calf compression and evaluation of added graduated static compression. *Acta Chir Scand*. 1986;152: 597-600.

55. Nicolaides AN, Fernandes e Fernandes J, Pollock AV. Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis. *Surgery*. 1980;87(1):69-76.

56. Nicolaides AN, Miles C, Hoare M, Jury P, Helmis E, Venniker R. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery*. 1983;94(1):21-25.

57. Norgren L, Austrell C, Brummer R, et al. Low incidence of deep vein thrombosis after total hip replacement: an interim analysis of patients on low molecular weight heparin vs sequential gradient compression prophylaxis. *Int Angiol*. 1996;1:11-14.

58. Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. *Int Angiol*. 1998;17(2):93-96.

59. Pietsch M, Kühle J, Hamer H, Pitto RP. Mechanical versus drug prevention of thrombosis after total hip endoprosthesis implantation. A randomized, controlled clinical study [in German]. *Biomed Tech (Berl)*. 2003;48(7-8):207-212.

60. Rasmussen A, Hansen PT, Lindholt J, et al. Venous thrombosis after abdominal surgery. A comparison between subcutaneous heparin and antithrombotic stockings, or both. *J Med*. 1988;19(3-4):193-201.

61. Santori FS, Vitullo A, Stopponi M, Santori N, Ghera S. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Joint Surg Br*. 1994;76(4):579-583.

62. Stannard JP, Harris RM, Bucknell AL, Cossi A, Ward J, Arrington ED. Prophylaxis of deep venous thrombosis after total hip arthroplasty by using intermittent compression of the plantar venous plexus. *Am J Orthop*. 1996;25(2):127-134.

63. Stone MH, Limb D, Campbell P, Stead D, Culleton G. A comparison of intermittent calf compression and enoxaparin for thromboprophylaxis in total hip replacement. A pilot study. *Int Orthop*. 1996;20(6):367-369.

64. Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *J Bone Joint Surg Am*. 1998;80(8):1158-1166.

65. Warwick D, Harrison J, Whitehouse S, Mitchelmore A, Thornton M. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. *J Bone Joint Surg Br*. 2002;84(3):344-350.

66. Yang BL, Zhang ZY, Guo SL. Clinical significance of preventive treatment of thrombosis for patients undergoing gynecological surgery with high risk factors [in Chinese]. *Zhonghua Fu Chan Ke Za Zhi*. 2009;44(8):570-573.

67. Clarke-Pearson DL, Synan IS, Dodge R, Soper JT, Berchuck A, Coleman RE. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *Am J Obstet Gynecol*. 1993;168(4):1146-1153, discussion 1153-1154.

68. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery*. 1998;43(5):1074-1081.

69. Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstet Gynecol*. 2001;98(6):989-995.

70. Murakami M, Wiley LA, Cindrick-Pounds L, Hunter GC, Uchida T, Killewich LA. External pneumatic compression does not increase urokinase plasminogen activator after abdominal surgery. *J Vasc Surg*. 2002;36(5):917-921.

71. Nagata C, Tanabe H, Takakura S, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. *J Obstet Gynaecol Res*. 2015;41(9):1440-1448.

72. Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. *Thromb Res*. 2010;125(3):e65-e70.

73. Spyropoulos AC, Hussein M, Lin J, Battleman D. Rates of symptomatic venous thromboembolism in US surgical patients: a retrospective administrative database study. *J Thromb Thrombolysis*. 2009;28(4):458-464.

74. Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *Br J Surg*. 1983;70(3):172-174.

75. Bachmann F, McKenna R, Meredith P, Carta S. Intermittent pneumatic compression of leg and thigh: a new successful method for the prevention of postoperative thrombosis [in German]. *Schweiz Med Wochenschr*. 1976;106(50):1819-1821.

76. Barnes RW, Brand RA, Clarke W, Hartley N, Hoak JC. Efficacy of graded-compression antiembolism stockings in patients undergoing total hip arthroplasty. *Clin Orthop Relat Res*. 1978; (132):61-67.

77. Butson AR. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. *Am J Surg*. 1981;142(4): 525-527.

78. Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. *J Orthop Trauma*. 1995;9(1):1-7.

79. Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement--the influence of preventive intermittent calf compression and of surgical technique. *Br J Surg*. 1983;70(1):17-19.

80. Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. *BMJ*. 1972; i(5793):131-135.

81. Holford CP. Graded compression for preventing deep venous thrombosis. *BMJ*. 1976;ii(6042):969-970.

82. Hui AC, Heras-Palou C, Dunn I, et al. Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement. *J Bone Joint Surg Br*. 1996;78(4):550-554.

83. Hull R, Delmore TJ, Hirsh J, et al. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thromb Res*. 1979;16(1-2):37-45.

84. Hull RD, Raskob GE, Gent M, et al. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. *JAMA*. 1990;263(17):2313-2317.

85. Marescaux J, Stemmer R, Plas A, Navarrete E, Petit B, Grenier JF. Importance of elastic compression of the lower limbs in the prevention of venous thrombosis in digestive surgery [in French]. *Phlebologie*. 1981;34(4):617-623.

86. Skillman JJ, Collins RE, Coe NP, et al. Prevention of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. *Surgery*. 1978;83(3):354-358.

87. Tsapogas MJ, Goussous H, Peabody RA, Karmody AM, Eckert C. Postoperative venous thrombosis and the effectiveness of prophylactic measures. *Arch Surg*. 1971;103(5):561-567.

88. Turner GM, Cole SE, Brooks JH. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis after major gynaecological surgery. *Br J Obstet Gynaecol*. 1984;91(6):588-591.

89. Turpie AG, Delmore T, Hirsh J, et al. Prevention of venous thrombosis by intermittent sequential calf compression in patients with intracranial disease. *Thromb Res*. 1979;15(5-6):611-616.

90. Turpie AG, Gallus A, Beattie WS, Hirsh J. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. *Neurology*. 1977;27(5):435-438.

91. Weitz J, Michelsen J, Gold K, Owen J, Carpenter D. Effects of intermittent pneumatic calf compression on postoperative thrombin and plasmin activity. *Thromb Haemost*. 1986;56(2):198-201.

92. Wilson NV, Das SK, Kakkar VV, et al. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. *J Bone Joint Surg Br*. 1992;74(1):50-52.

93. Clarke-Pearson DL, Creasman WT, Coleman RE, Synan IS, Hinshaw WM. Perioperative external pneumatic calf compression as thromboembolism prophylaxis in gynecologic oncology: report of a randomized controlled trial. *Gynecol Oncol*. 1984;18(2):226-232.

94. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med*. 1989;149(3):679-681.

95. Caprini JA, Chucker JL, Zuckerman L, Vagher JP, Franck CA, Cullen JE. Thrombosis prophylaxis using external compression. *Surg Gynecol Obstet*. 1983; 156(5):599-604.

96. Goldhaber SZ, Hirsch DR, MacDougall RC, Polak JF, Creager MA, Cohn LH. Prevention of venous thrombosis after coronary artery bypass surgery (a randomized trial comparing two mechanical prophylaxis strategies). *Am J Cardiol*. 1995;76(14):993-996.

97. Pedegana LR, Burgess EM, Moore AJ, Carpenter ML. Prevention of thromboembolic disease by external pneumatic compression in patients undergoing total hip arthroplasty. *Clin Orthop Relat Res*. 1977; (128):190-193.

98. Ryan MG, Westrich GH, Potter HG, et al. Effect of mechanical compression on the prevalence of proximal deep venous thrombosis as assessed by magnetic resonance venography. *J Bone Joint Surg Am*. 2002;84(11):1998-2004.

99. Silbersack Y, Taute BM, Hein W, Podhaisky H. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. *J Bone Joint Surg Br*. 2004;86(6):809-812.

100. Sobieraj-Teague M, Hirsh J, Yip G, et al. Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients. *J Thromb Haemost*. 2012;10(2):229-235.

101. Van Arsdalen KN, Barnes RW, Clarke G, Smith MJ, Koontz WW Jr. Deep vein thrombosis and prostatectomy. *Urology*. 1983;21(5):461-463.

102. Bucci MN, Papadopoulos SM, Chen JC, Campbell JA, Hoff JT. Mechanical prophylaxis of venous thrombosis in patients undergoing craniotomy: a randomized trial. *Surg Neurol*. 1989;32(4):285-288.

103. Hansberry KL, Thompson IM Jr, Bauman J, Deppe S, Rodriguez FR. A prospective comparison of thromboembolic stockings, external sequential pneumatic compression stockings and heparin sodium/dihydroergotamine mesylate for the prevention of thromboembolic complications in urological surgery. *J Urol*. 1991;145(6):1205-1208.

104. Cohen AT, Skinner JA, Warwick D, Brenkel I. The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. *J Bone Joint Surg Br*. 2007;89(7):887-892.

105. Edwards JZ, Pulido PA, Ezzet KA, Copp SN, Walker RH, Colwell CW Jr. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. *J Arthroplasty*. 2008;23(8):1122-1127.

106. Eisele R, Kinzl L, Koelsch T. Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis. *J Bone Joint Surg Am*. 2007; 89(5):1050-1056.

107. Ivanic GM, Moser I, Homann NC, Pietsch M, Kriechhammer P, Hennerbichler A. Intermittent compression devices for swelling reduction and thrombosis prophylaxis—a pilot study after total hip replacement. Is the 2 hour daily minimum application sufficient? [in German]. *Unfallchirurg*. 2006;109(9):786-792.

108. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, et al. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *Int Angiol*. 1996;15(2):162-168.

109. Lieberman JR, Huo MM, Hanway J, Salvati EA, Sculco TP, Sharrock NE. The prevalence of deep venous thrombosis after total hip arthroplasty with hypotensive epidural anesthesia. *J Bone Joint Surg Am*. 1994;76(3):341-348.

110. Patel A, Couband D, Féron JM, Signoret F. Prevention of deep venous thrombosis in arthroplastic surgery of the hip by the combination of heparinotherapy and the antithrombosis stocking [in French]. *Presse Med*. 1988;17(23):1201-1203.

111. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest*. 1996;109(1):82-85.

112. Sakai T, Izumi M, Kumagai K, et al. Effects of a foot pump on the incidence of deep vein thrombosis after total knee arthroplasty in patients given edoxaban: a randomized controlled study. *Medicine (Baltimore)*. 2016;95(1):e2247.

113. Siragusa S, Vicentini L, Carbone S, Barone M, Beltrametti C, Piovella F. Intermittent pneumatic leg compression (IPLC) and unfractionated heparin (UFH) in the prevention of post-operative deep vein thrombosis in hip surgery: a randomized clinical trial. *Br J Haematol*. 1994;87(suppl 1):186.

114. Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. *J Bone Joint Surg Am*. 1996;78(6):826-834.

115. Wille-Jørgensen P, Hauch O, Dimo B, Christensen SW, Jensen R, Hansen B. Prophylaxis of deep venous thrombosis after acute abdominal operation. *Surg Gynecol Obstet*. 1991;172(1):44-48.

116. Wille-Jørgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. *Br J Surg*. 1985;72(7):579-581.

117. Windisch C, Kolb W, Kolb K, Grützner P, Venbrocks R, Anders J. Pneumatic compression with foot pumps facilitates early postoperative mobilisation in total knee arthroplasty. *Int Orthop*. 2011;35(7):995-1000.

118. Baca I, Schneider B, Köhler T, Misselwitz F, Zehle A, Mühe F. Prevention of thromboembolism in minimal invasive interventions and brief inpatient treatment. Results of a multicenter, prospective, randomized, controlled study with a low molecular weight heparin [in German]. *Chirurg*. 1997;68(12):1275-1280.

119. Hume M, Kuriakose TX, Zuch L, Turner RH. 125I fibrinogen and the prevention of venous thrombosis. *Arch Surg*. 1973;107(5):803-806.

120. Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthop Scand*. 1991;62(1):33-38.

121. Levine MN, Gent M, Hirsh J, et al. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Intern Med*. 1996;156(8):851-856.

122. Nicolaides AN, Dupont PA, Desai S, et al. Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. *Lancet*. 1972;ii(7783):890-893.

123. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. *Spine*. 1996;21(7):853-858, discussion 859.

124. Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K; Arar Study Group. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. *Br J Anaesth*. 1997;78(6):660-665.

125. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. *J Thromb Haemost*. 2007;5(9):1854-1861.

126. Woolson ST, Watt JM. Intermittent pneumatic compression to prevent proximal deep venous thrombosis during and after total hip replacement. A prospective, randomized study of compression alone, compression and aspirin, and compression and low-dose warfarin. *J Bone Joint Surg Am*. 1991;73(4):507-512.

127. Yokote R, Matsubara M, Hirasawa N, Hagio S, Ishii K, Takata C. Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population? *J Bone Joint Surg Br*. 2011;93(2):251-256.

128. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med*. 1998;339(2):80-85.

129. Bigg SW, Catalona WJ. Prophylactic mini-dose heparin in patients undergoing radical retropubic prostatectomy. A prospective trial. *Urology*. 1992;39(4):309-313.

130. Nurmohamed MT, van Riel AM, Henkens CM, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost*. 1996;75(2):233-238.

131. Song KY, Yoo HM, Kim EY, et al. Optimal prophylactic method of venous thromboembolism for gastrectomy in Korean patients: an interim analysis of prospective randomized trial. *Ann Surg Oncol*. 2014;21(13):4232-4238.

132. Maksimovic ZV, Lausevic Z, Kostic R, Kolic Z, Petrovic G, Sego D. Medicamentous prophylaxis of deep vein thrombosis in emergency surgical patients. *Int Angiol*. 1996;15(2 Suppl 1):31.

133. Halim TA, Chhabra HS, Arora M, Kumar S. Pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury: an Indian perspective. *Spinal Cord*. 2014;52(7):547-550.

134. Jung YJ, Seo HS, Park CH, et al. Venous thromboembolism incidence and prophylaxis use after gastrectomy among Korean patients with gastric adenocarcinoma: the PROTECTOR randomized clinical trial. *JAMA Surg*. 2018;153(10):939-946.

135. Hamidi S, Riazi M. Incidence of venous thromboembolic complications in instrumental spinal surgeries with preoperative chemoprophylaxis. *J Korean Neurosurg Soc*. 2015;57(2):114-118.

136. Zheng H, Gao Y, Yan X, Gao M, Gao W. Prophylactic use of low molecular weight heparin in combination with graduated compression stockings in post-operative patients with gynecologic cancer [in Chinese]. *Zhonghua Zhong Liu Za Zhi*. 2014;36(1):39-42.

137. Haut ER, Garcia LJ, Shihab HM, et al. The effectiveness of prophylactic inferior vena cava filters in trauma patients: a systematic review and meta-analysis. *JAMA Surg*. 2014;149(2):194-202.

138. Kaw R, Pasupuleti V, Wayne Overby D, et al. Inferior vena cava filters and postoperative outcomes in patients undergoing bariatric surgery: a meta-analysis. *Surg Obes Rel Dis*. 2014;10(4):725-733.

139. Birkmeyer NJ, Finks JF, English WJ, et al; Michigan Bariatric Surgery Collaborative. Risks and benefits of prophylactic inferior vena cava filters in patients undergoing bariatric surgery. *J Hosp Med*. 2013;8(4):173-177.

140. Gargiulo NJ III, Veith FJ, Lipsitz EC, Suggs WD, Ohki T, Goodman E. Experience with inferior vena cava filter placement in patients undergoing open gastric bypass procedures. *J Vasc Surg*. 2006;44(6):1301-1305.

141. Gorman PH, Qadri SF, Rao-Patel A. Prophylactic inferior vena cava (IVC) filter placement may increase the relative risk of deep venous thrombosis after acute spinal cord injury. *J Trauma*. 2009;66(3):707-712.

142. Gosin JS, Graham AM, Ciocca RG, Hammond JS. Efficacy of prophylactic vena cava filters in high-risk trauma patients. *Ann Vasc Surg*. 1997;11(1):100-105.

143. Halmi D, Kolesnikov E. Preoperative placement of retreivable inferior vena cava filters in bariatric surgery. *Surg Obes Relat Dis*. 2007;3(6):602-605.

144. Hemmila MR, Osborne NH, Henke PK, et al. Prophylactic inferior vena cava filter placement does not result in a survival benefit for trauma patients. *Ann Surg*. 2015;262(4):577-585.

145. Khansarinia S, Dennis JW, Veldenz HC, Butcher JL, Hartland L. Prophylactic Greenfield filter placement in selected high-risk trauma patients. *J Vasc Surg*. 1995;22(3):231-235, discussion 235-236.

146. Li W, Gorecki P, Semaan E, Briggs W, Tortolani AJ, D'Ayala M. Concurrent prophylactic placement of inferior vena cava filter in gastric bypass and adjustable banding operations in the Bariatric Outcomes Longitudinal Database. *J Vasc Surg*. 2012;55(6):1690-1695.

147. Obeid FN, Bowling WM, Fike JS, Durant JA. Efficacy of prophylactic inferior vena cava filter placement in bariatric surgery. *Surg Obes Rel Dis*. 2007;3(6):606-608; discussion 609-610.

148. Overby DW, Kohn GP, Cahan MA, et al. Risk-group targeted inferior vena cava filter placement in gastric bypass patients. *Obes Surg*. 2009;19(4):451-455.

149. Ozturk C, Ganiyusufoglu K, Alanay A, Aydogan M, Onat L, Hamzaoglu A. Efficacy of prophylactic placement of inferior vena cava filter in patients undergoing spinal surgery. *Spine*. 2010;35(20):1893-1896.

150. Rajasekhar A, Lottenberg L, Lottenberg R, et al. A pilot study on the randomization of inferior vena cava filter placement for venous thromboembolism prophylaxis in high-risk trauma patients. *J Trauma*. 2011;71(2):323-328, discussion 328-329.

151. Rodriguez JL, Lopez JM, Proctor MC, et al. Early placement of prophylactic vena caval filters in injured patients at high risk for pulmonary embolism. *J Trauma*. 1996;40(5):797-802, discussion 802-804.

152. Rogers FB, Shackford SR, Ricci MA, Huber BM, Atkins T. Prophylactic vena cava filter insertion in selected high-risk orthopaedic trauma patients. *J Orthop Trauma*. 1997;11(4):267-272.

153. Benevenia J, Bibbo C, Patel DV, Grossman MG, Bahramipour PF, Pappas PJ. Inferior vena cava filters prevent pulmonary emboli in patients with metastatic pathologic fractures of the lower extremity. *Clin Orthop Relat Res*. 2004;426:87-91.

154. Bikdeli B, Chatterjee S, Desai NR, et al. Inferior vena cava filters to prevent pulmonary embolism: systematic review and meta-analysis. *J Am Coll Cardiol*. 2017;70(13):1587-1597.

155. Ho KM, Rao S, Honeybul S, et al. A multicenter trial of vena cava filters in severely injured patients. *N Engl J Med*. 2019;381(4):328-337.

156. Agency for Healthcare Research and Quality. Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations. Comparative Effectiveness Review No. 116. AHRQ Publication No. 13-EHC082-1. Available at: https://www.ncbi.nlm.nih.gov/books/NBK148555/pdf/Bookshelf_NBK148555.pdf. Accessed 16 July 2018.

157. Rasmussen MS, Jørgensen LN, Wille-Jørgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev*. 2009;(1):CD004318.

158. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev*. 2018;11:CD004318.

159. Sobieraj DM, Lee S, Coleman CI, et al. Prolonged versus standard-duration venous thromboprophylaxis in major orthopedic surgery: a systematic review. *Ann Intern Med*. 2012;156(10):720-727.

160. Huo MH, Muntz J. Extended thromboprophylaxis with low-molecular-weight heparins after hospital discharge in high-risk surgical and medical patients: a review. *Clin Ther*. 2009;31(6):1129-1141.

161. Lu X, Lin J. Low molecular weight heparin versus other anti-thrombotic agents for prevention of venous thromboembolic events after total hip or total knee replacement surgery: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2018;19(1):322.

162. Milinis K, Shalhoub J, Coupland AP, Salciccioli JD, Thapar A, Davies AH. The effectiveness of graduated compression stockings for prevention of venous thromboembolism in orthopedic and abdominal surgery patients requiring extended pharmacologic thromboprophylaxis. *J Vasc Surg Venous Lymphat Disord*. 2018;6(6):766-777.e2.

163. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001;358(9275):9-15.

164. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135(10):858-869.

165. O'Donnell M, Linkins LA, Kearon C, Julian J, Hirsh J. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med*. 2003;163(11):1362-1366.

166. Bergqvist D, Benoni G, Björgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med*. 1996;335(10):696-700.

167. Hull RD, Pineo GF, Francis C, et al; North American Fragmin Trial Investigators. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med*. 2000;160(14):2208-2215.

168. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty--the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res*. 1998;89(6):281-287.

169. Manganelli D, Pazzagli M, Mazzantini D, et al. Prolonged prophylaxis with unfractioned heparin is effective to reduce delayed deep vein thrombosis in total hip replacement. *Respiration*. 1998;65(5):369-374.

170. Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med*. 2002;162(17):1966-1971.

171. Bergqvist D, Agnelli G, Cohen AT, et al; ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002;346(13):975-980.

172. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, et al; FAME Investigators. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemost*. 2006;4(11): 2384-2390.

173. Eriksson BI, Lassen MR; PENTasaccharide in HIp-FRActure Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2003;163(11):1337-1342.

174. Andersen BS. Postoperative activation of the haemostatic system--influence of prolonged thromboprophylaxis in patients undergoing total hip arthroplasty. *Haemostasis*. 1997;27(5):219-227.

175. Nilsson PE, Bergqvist D, Benoni G, et al. The post-discharge prophylactic management of the orthopedic patient with low-molecular-weight heparin: enoxaparin. *Orthopedics*. 1997;20:22-25.

176. Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery--results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost*. 1997;77(1):26-31.

177. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet*. 1996;348(9022):224-228.

178. Comp PC, Spiro TE, Friedman RJ, et al; Enoxaparin Clinical Trial Group. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *J Bone Joint Surg Am*. 2001;83(3):336-345.

179. Lausen I, Jensen R, Jorgensen LN, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg*. 1998;164(9):657-663.

180. Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2008;372(9632):31-39.

181. Auer R, Scheer A, Wells PS, et al. The use of extended perioperative low molecular weight heparin (tinzaparin) to improve disease-free survival following surgical resection of colon cancer: a pilot randomized controlled trial. *Blood Coagul Fibrinolysis*. 2011;22(8):760-762.

182. Kolb G, Bodamer I, Galster H, et al; Long-term Thromboprophylaxis Study Group. Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thromb Haemost*. 2003;90(6):1100-1105.

183. Kakkar VV, Balibrea JL, Martínez-González J, Prandoni P; CANBESURE Study Group. Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. *J Thromb Haemost*. 2010;8(6):1223-1229.

184. Vedovati MC, Becattini C, Rondelli F, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Ann Surg*. 2014;259(4):665-669.

185. Chen D, Xue Y, Jia S. Efficacy and safety of rivaroxaban in preventing deep venous thromboembolism after major orthopedic operations. *Int J Clin Exp Med*. 2016;9(2):4077-4082.

186. Bauer KA, Eriksson BI, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med*. 2001;345(18):1305-1310.

187. Colwell CW Jr, Kwong LM, Turpie AG, Davidson BL. Flexibility in administration of fondaparinux for prevention of symptomatic venous thromboembolism in orthopaedic surgery. *J Arthroplasty*. 2006;21(1):36-45.

188. Turpie AG, Bauer KA, Eriksson BI, Lassen MR; PENTATHALON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial [published correction appears in *Lancet*. 2002;360(9339):1102]. *Lancet*. 2002;359(9319):1721-1726.

189. Turpie AG, Fisher WD, Bauer KA, et al; OdiXa-Knee Study Group. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost*. 2005;3(11):2479-2486.

190. Turpie AG, Lassen MR, Davidson BL, et al; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009;373(9676):1673-1680.

191. Ginsberg JS, Davidson BL, Comp PC, et al; RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty*. 2009;24(1):1-9.

192. Paikin JS, Hirsh J, Chan NC, Ginsberg JS, Weitz JI, Eikelboom JW. Timing the first postoperative dose of anticoagulants: lessons learned from clinical trials. *Chest*. 2015;148(3):587-595.

193. Alfaro MJ, Páramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost*. 1986;56(1):53-56.

194. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. *Chin Med J (Engl)*. 2014;127(12):2201-2205.

195. Josefsson G, Dahlqvist A, Bodfors B. Prevention of thromboembolism in total hip replacement. Aspirin versus dihydroergotamine-heparin. *Acta Orthop Scand*. 1987;58(6):626-629.

196. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. *J Arthroplasty*. 2013; 28(10):1868-1873.

197. Lotke PA, Palevsky H, Keenan AM, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop Relat Res*. 1996;324: 251-258.

198. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. *J Arthroplasty*. 2006;21(6 Suppl 2):139-143.

199. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. *Blood Coagul Fibrinolysis*. 2014;25(7):660-664.

200. Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med*. 2013;158(11):800-806.

201. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. *N Engl J Med*. 2018;378(8):699-707.

202. Jameson SS, Baker PN, Charman SC, et al. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after knee replacement: a non-randomised comparison using National Joint Registry Data. *J Bone Joint Surg Br*. 2012;94(7):914-918.

203. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: a non-randomised comparison from information in the National Joint Registry. *J Bone Joint Surg Br*. 2011;93(11):1465-1470.

204. Neumann I, Rada G, Claro JC, et al. Oral direct Factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(10):710-719.

205. Eriksson BI, Dahl OE, Huo MH, et al; RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost*. 2011;105(4):721-729.

206. Eriksson BI, Dahl OE, Rosencher N, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007;5(11):2178-2185.

207. Eriksson BI, Dahl OE, Rosencher N, et al; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet*. 2007;370(9591):949-956.

208. Mirdamadi A, Dashtkar S, Kaji M, Pazhang F, Haghpanah B, Gharipour M. Dabigatran versus enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: a randomized clinical trial. *ARYA Atheroscler*. 2014;10(6):292-297.

209. Eriksson BI, Borris L, Dahl OE, et al; ODIXa-HIP Study Investigators. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost*. 2006;4(1):121-128.

210. Eriksson BI, Borris LC, Dahl OE, et al. Dose-escalation study of rivaroxaban (BAY 59-7939)--an oral, direct factor Xa inhibitor--for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Res*. 2007;120(5):685-693.

211. Eriksson BI, Borris LC, Dahl OE, et al; ODIXa-HIP Study Investigators. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation*. 2006;114(22):2374-2381.

212. Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358(26):2765-2775.

213. Zhang W, Wang D, Sun H, Li S, Liu L. Efficacy and safety of rivaroxaban in the prevention of deep vein thrombosis after hip arthroplasty. *Chin J Tissue Eng Res*. 2013;17(30):5440-5445.

214. Kim SM, Moon YW, Lim SJ, Kim DW, Park YS. Effect of oral factor Xa inhibitor and low-molecular-weight heparin on surgical complications following total hip arthroplasty. *Thromb Haemost*. 2016;115(3):600-607.

215. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776-2786.

216. Silva-Kanan P, Schwartsmann C, Carbonera L, Conrad S, Faria M. Comparative study between rivaroxaban and enoxaparin in deep venous thromboembolism prophylaxis in patients submitted to total hip arthroplasty. *Rev Bras Ortop*. 2008;43(8):319-328.

217. Singh S, Kallhfallah A. The PREVENT Trial – prevention of venous thromboembolism with enoxaparin vs rivaroxaban following hip and knee replacement surgeries. *Intern Med J*. 2012;42(suppl 2):14-22.

218. Hu Y, Peng D, Shen Y, Chen X. Different anticoagulant drugs during knee joint replacement: changes of hemorheology. *Chin J Tissue Eng Res*. 2015; 19(13):2023-2027.

219. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost*. 2007;5(12):2368-2375.

220. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363(26):2487-2498.

221. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807-815.

222. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med*. 2009;361(6):594-604.

223. Eriksson BI, Agnelli G, Gallus AS, et al. Darexaban (YM150) versus enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a randomised phase IIb dose confirmation study (ONYX-3). *Thromb Haemost*. 2014;111(2):213-225.

224. Eriksson BI, Turpie AG, Lassen MR, et al; ONYX study group. A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery. *J Thromb Haemost*. 2007;5(8):1660-1665.

225. Eriksson BI, Turpie AG, Lassen MR, et al; ONYX-2 STUDY GROUP. Prevention of venous thromboembolism with an oral factor Xa inhibitor, YM150, after total hip arthroplasty. A dose finding study (ONYX-2). *J Thromb Haemost*. 2010;8(4):714-721.

226. Fuji T, Nakamura M, Takeuchi M. Darexaban for the prevention of venous thromboembolism in Asian patients undergoing orthopedic surgery: results from 2 randomized, placebo-controlled, double-blind studies. *Clin Appl Thromb/Hemost*. 2014;20(2):199-211.

227. Fuji T, Fujita S, Kawai Y, et al. Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V. *Thromb J*. 2015;13(1):27.

228. Fuji T, Fujita S, Kawai Y, et al. Safety and efficacy of edoxaban in patients undergoing hip fracture surgery. *Thromb Res*. 2014;133(6):1016-1022.

229. Fuji T, Wang CJ, Fujita S, Kawai Y, Kimura T, Tachibana S. Safety and efficacy of edoxaban, an oral factor xa inhibitor, for thromboprophylaxis after total hip arthroplasty in Japan and Taiwan. *J Arthroplasty*. 2014;29(12):2439-2446.

230. Fuji T, Wang CJ, Fujita S, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. *Thromb Res*. 2014;134(6):1198-1204.

231. Raskob G, Cohen AT, Eriksson BI, et al. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study. *Thromb Haemost*. 2010;104(3):642-649.

232. Agnelli G, Haas S, Ginsberg JS, Krueger KA, Dmitrienko A, Brandt JT. A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement. *J Thromb Haemost*. 2007;5(4):746-753.

233. Cohen AT, Boyd RA, Mandema JW, Dicarlo L, Pak R; A5571010 Investigators. An adaptive-design dose-ranging study of PD 0348292, an oral factor Xa inhibitor, for thromboprophylaxis after total knee replacement surgery. *J Thromb Haemost*. 2013;11(8):1503-1510.

234. Turpie AG, Bauer KA, Davidson BL, et al; EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). *Thromb Haemost*. 2009;101(1):68-76.

235. Weitz JI, Cao C, Eriksson BI, et al. A dose-finding study with TAK-442, an oral factor Xa inhibitor, in patients undergoing elective total knee replacement surgery. *Thromb Haemost*. 2010;104(6):1150-1157.

236. Agency for Healthcare Research and Quality. Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update. Comparative Effectiveness Review No. 191. AHRQ Publication No. 17-EHC021-EF. Available at: https://effectivehealthcare.ahrq.gov/products/thromboembolism-update/research-2017. Accessed 16 July 2018.

237. Fitzgerald RH Jr, Spiro TE, Trowbridge AA, et al; Enoxaparin Clinical Trial Group. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am*. 2001;83(6):900-906.

238. Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med*. 1993;329(19):1370-1376.

239. Hull RD, Pineo GF, Francis C, et al; The North American Fragmin Trial Investigators. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med*. 2000;160(14):2199-2207.

240. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med*. 1996;124(7):619-626.

241. Francis CW, Pellegrini VD Jr, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. *J Bone Joint Surg Am*. 1997;79(9):1365-1372.

242. Avikainen V, von Bonsdorff H, Partio E, et al. Low molecular weight heparin (enoxaparin) compared with unfractionated heparin in prophylaxis of deep venous thrombosis and pulmonary embolism in patients undergoing hip replacement. *Ann Chir Gynaecol*. 1995;84(1):85-90.

243. Barre J, Pfister G, Potron G, et al. Comparison of the efficacy and tolerance of Kabi 2165 and standard heparin in the prevention of deep venous thrombosis in total hip prosthesis [in French]. *J Mal Vasc*. 1987;12(suppl B):90-95.

244. Colwell CW Jr, Spiro TE, Trowbridge AA, et al; Enoxaparin Clinical Trial Group. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety [published correction appears in *J Bone Joint Surg Am*. 1994;76(3):4741]. *J Bone Joint Surg Am*. 1994;76(1):3-14.

245. Colwell CW Jr, Spiro TE, Trowbridge AA, Stephens JW, Gardiner GA Jr, Ritter MA; Enoxaparin Clinical Trial Group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. *Clin Orthop Relat Res*. 1995;(321):19-27.

246. Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis*. 1989;19(1):5-12.

247. Eriksson BI, Kälebo P, Anthymyr BA, Wadenvik H, Tengborn L, Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. *J Bone Joint Surg Am*. 1991;73(4):484-493.

248. Faunø P, Suomalainen O, Rehnberg V, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. *J Bone Joint Surg Am*. 1994;76(12):1814-1818.

249. Levine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med*. 1991;114(7):545-551.

250. Menzin J, Richner R, Huse D, Colditz GA, Oster G. Prevention of deep-vein thrombosis following total hip replacement surgery with enoxaparin versus unfractionated heparin: a pharmacoeconomic evaluation. *Ann Pharmacother*. 1994;28(2):271-275.

251. Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost*. 1988;60(3):407-410.

252. Schwartsmann C, Cavalieri C, Drumond S. Randomized, comparative, open study to assess the efficacy and safety of enoxaparin compared with unfractionated heparin in the prophylaxis of venous thromboembolism in patients undergoing total hip arthroplasty. *Rev Bras Ortop*. 1996;(31): 797-808.

253. Senaran H, Acaroğlu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. *Arch Orthop Trauma Surg*. 2006;126(1):1-5.

254. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev*. 2002; (4):CD000305.

255. Galasko CS, Edwards DH, Fearn CB, Barber HM. The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. *Acta Orthop Scand*. 1976;47(3):276-282.

256. Jørgensen PS, Knudsen JB, Broeng L, et al. The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. *Clin Orthop Relat Res*. 1992;278:95-100.

257. Kew J, Lee YL, Davey IC, Ho SY, Fung KC, Metreweli C. Deep vein thrombosis in elderly Hong Kong Chinese with hip fractures detected with compression ultrasound and Doppler imaging: incidence and effect of low molecular weight heparin. *Arch Orthop Trauma Surg*. 1999;119(3-4): 156-158.

258. Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in hip-fracture patients. Comparison of low-dose heparin and low-molecular-weight heparin combined with dihydroergotamine. *Arch Orthop Trauma Surg*. 1989;108(1):10-13.

259. Moskovitz PA, Ellenberg SS, Feffer HL, et al. Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *J Bone Joint Surg Am*. 1978;60(8):1065-1070.

260. Agnelli G, Cosmi B, Di Filippo P, et al. A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. *Thromb Haemost*. 1992;67(2):203-208.

261. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000; 355(9212):1295-1302.

262. Barrie WW, Wood EH, Crumlish P, Forbes CD, Prentice CR. Low-dosage ancrod for prevention of thrombotic complications after surgery for fractured neck of femur. *BMJ*. 1974;iv(5937):130-133.

263. Hamilton HW, Crawford JS, Gardiner JH, Wiley AM. Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. *J Bone Joint Surg Br*. 1970;52(2):268-289.

264. Li T, Lv M, Li Q. Comprehensive prophylaxis for deep venous thrombosis after proximal femur fractures in geriatric patients [in Chinese]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2008;22(4):453-455.

265. Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med*. 1989;149(4):771-774.

266. Sasaki S, Miyakoshi N, Matsuura H, et al. Prospective study on the efficacies of fondaparinux and enoxaparin in preventing venous thromboembolism after hip fracture surgery. *J Orthop Sci*. 2011;16(1):64-70.

267. Gao Y, Long A, Xie Z, et al. The compliance of thromboprophylaxis affects the risk of venous thromboembolism in patients undergoing hip fracture surgery. *Springerplus*. 2016;5(1):1362.

268. Monreal M, Lafoz E, Navarro A, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma*. 1989;29(6):873-875.

269. Pini M, Tagliaferri A, Manotti C, Lasagni F, Rinaldi E, Dettori AG. Low molecular weight heparin (Alfa LHWH) compared with unfractionated heparin in prevention of deep-vein thrombosis after hip fractures. *Int Angiol*. 1989;8(3):134-139.

270. Platz A, Hoffmann R, Kohler A, Bischof T, Trentz O. Prevention of thromboembolism in hip fracture: unfractionated heparin versus low molecular weight heparin (a prospective, randomized study) [in German]. *Z Unfallchir Versicherungsmed*. 1993;86(3):184-188.

271. Drummond M, Aristides M, Davies L, Forbes C. Economic evaluation of standard heparin and enoxaparin for prophylaxis against deep vein thrombosis in elective hip surgery. *Br J Surg*. 1994;81(12):1742-1746.

272. Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg*. 2001;88(7):913-930.

273. Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). *Thromb Haemost*. 1989;62(4):1046-1049.

274. Pezzuoli G, Neri Serneri GG, Settembrini P, et al; STEP-Study Group. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). *Int Surg*. 1989; 74(4):205-210.

275. Bergqvist D, Flordal PA, Friberg B, et al. Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. *Vasa*. 1996;25(2):156-160.

276. Kakkar VV, Corrigan T, Fossard DP, et al. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *Lancet*. 1975;ii(7924):45-51.

277. The Multicenter Trial Committee. Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis. A multicenter trial [published correction appears in *JAMA*. 1984;252(10):1283]. *JAMA*. 1984;251(22):2960-2966.

278. Groote Schuur Hospital Thromboembolus Study Group. Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: interim report of prospective trial. *Br Med J*. 1979;1(6176):1447-1450.
279. Bates T. Trial of a single low dose of heparin in the prevention of post-operative deep-vein thrombosis monitored by doppler ultrasound. *Postgrad Med J*. 1974;50(581):135-139.
280. Bejjani BB, Chen DC, Nolan NG, Edson M. Minidose heparin in transurethral prostatectomy. *Urology*. 1983;22(3):251-254.
281. Bergström K, Lahnborg G. The effect of major surgery, low doses of heparin and thromboembolism on plasma antithrombin. Comparison of immediate thrombin inhibiting capacity and the antithrombin III content. *Thromb Res*. 1975;6(3):223-233.
282. Breddin K, Häring R, Koppenhagen K. Prevention of postoperative thrombotic complications with heparin and dihydroergotamine. A randomized double-blind study [in German]. *Dtsch Med Wochenschr*. 1983;108(3):98-102.
283. Clagett GP, Brier DF, Rosoff CB, Schneider PB, Salzman EW. Effect of aspirin on postoperative platelet kinetics and venous thrombosis. *Surg Forum*. 1974;25(0):473-476.
284. Covey TH, Sherman L, Baue AE. Low-dose heparin in postoperative patients: a prospective, coded study. *Arch Surg*. 1975;110(8):1021-1026.
285. Eikelboom JW, Kearon C, Guyatt G, et al. Perioperative aspirin for prevention of venous thromboembolism: the PeriOperative ISchemia Evaluation-2 Trial and a pooled analysis of the randomized trials. *Anesthesiology*. 2016;125(6):1121-1129.
286. Hör G, Buttermann G, Theisinger W, Pabst HW. Prevention of postoperative thromboembolism by various treatments. Controlled clinical trial in 632 patients using 125I-fibrinogen uptake test and lung perfusion scans in patients with deep venous thrombosis. *Eur J Nucl Med*. 1976;1(4):197-203.
287. Joffe S. Drug prevention of postoperative deep vein thrombosis. A compararative study of calcium heparinate and sodium pentosan polysulfate. *Arch Surg*. 1976;111(1):37-40.
288. Jones DP, Byrne P, Mackenzie R, Ameli FM, Provan JL.Intraoperative single-dose heparin prophylaxis against deep-vein thrombosis. *Can J Surg*. 1984; 27(1):15-16.
289. Kakkar VV, Corrigan T, Spindler J, et al. Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery. A double-blind, randomised trial. *Lancet*. 1972;ii(7768):101-106.
290. Kiil J, Møoller JC. Postoperative deep vein thrombosis of the lower limb and prophylactic value of heparin evaluated by phlebography. *Acta Radiol Diagn (Stockh)*. 1979;20(3):507-512.
291. Lahnborg G, Bergström K. Clinical and haemostatic parameters related to thromboembolism and low-dose heparin prophylaxis in major surgery. *Acta Chir Scand*. 1975;141(7):590-595.
292. Lareng L, Vaysse C, Plante J, Boneu B, Gouzi M. Prevention of postoperative thromboembolic disease in general surgery: a randomized trial of 2 therapeutic procedures evaluated by the labelled fibrinogen method [in French]. *Anesth Analg (Paris)*. 1978;35(6):1185-1193.
293. Kraytman M, Kutnowski M, Ansay J, Fastrez R. Prophylaxis of postoperative deep vein thromboses by means of weak doses of subcutaneous heparin [in French]. *Acta Chir Belg*. 1976;75(5):519-529.
294. MacCallum PK, Thomson JM, Poller L. Effects of fixed minidose warfarin on coagulation and fibrinolysis following major gynaecological surgery. *Thromb Haemost*. 1990;64(4):511-515.
295. Osman Y, Kamal M, Soliman S, Sheashaa H, Shokeir A, Shehab el-Dein AB. Necessity of routine postoperative heparinization in non-risky live-donor renal transplantation: results of a prospective randomized trial. *Urology*. 2007;69(4):647-651.
296. Propsting J, Williams O, Stathis M, McCaffrey JF. The prophylazis of deep vein thrombosis with low-dose heparin: a trial. *Aust N Z J Surg*. 1974;44(3): 289-291.
297. Roberts VC, Cotton LT. Failure of low-dose heparin to improve efficacy of peroperative intermittent calf compression in preventing postoperative deep vein thrombosis. *BMJ*. 1975;iii(5981):458-460.
298. Rosenberg IL, Evans M, Pollock AV. Prophylaxis of postoperative leg vine thrombosis by low dose subcutaneous heparin or peroperative calf muscle stimulation: a controlled clinical trial. *BMJ*. 1975;i(5959):649-651.
299. Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. *BMJ*. 1975;iv(5991):257-259.
300. Strand L, Bank-Mikkelsen OK, Lindewald H. Small heparin doses as prophylaxis against deep-vein thrombosis in major surgery. *Acta Chir Scand*. 1975; 141(7):624-627.
301. Studer-Schär A. Hemorrhages caused by "low dose" heparin and placebo (NaCl solution) in surgical gynecology [in German]. *Gynakol Rundsch*. 1982; 22(4):241-248.
302. Williams HT. Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. *Lancet*. 1971;ii(7731):950-952.
303. Akl EA, Kahale L, Sperati F, et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. *Cochrane Database Syst Rev*. 2014;(6):CD009447.
304. Barbui T, Cassinelli G, Cortellazzo S, et al. Comparison of low molecular weight heparin CY 216 and unfractionated heparin in preventing post-operative venous thromboembolism in general surgery: a preliminary results of a cooperative study. *Fibrinolysis*. 1990;4:79.
305. Baumgartner A, Jacot N, Moser G, Krähenbühl B. Prevention of postoperative deep vein thrombosis by one daily injection of low molecular weight heparin and dihydroergotamine. *Vasa*. 1989;18(2):152-156.
306. Baykal C, Al A, Demirtaş E, Ayhan A. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind clinical study. *Eur J Gynaecol Oncol*. 2001;22(2):127-130.
307. ENOXACAN Study Group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. *Br J Surg*. 1997;84(8):1099-1103.

308. Bergqvist D, Burmark U, Frisell J, et al. Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. *Semin Thromb Hemost*. 1990;16 suppl:19-24.

309. Bergqvist D, Burmark US, Frisell J, et al. Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg*. 1986;73(3):204-208.

310. Caen JP. A randomized double-blind study between a low molecular weight heparin Kabi 2165 and standard heparin in the prevention of deep vein thrombosis in general surgery. A French multicenter trial. *Thromb Haemost*. 1988;59(2):216-220.

311. Catania G, Salanitri G. Prevention of postoperative deep vein thrombosis by two different heparin types. *Int J Clin Pharmacol Ther Toxicol*. 1988;26(6): 304-309.

312. Creperio G, Marabini M, Ciocia G, Bergonzi M, Fincato M. Evaluation of the effectiveness and safety of Fragmin (Kabi 2165) versus calcium heparin in the prevention of deep venous thrombosis in general surgery [in Italian]. *Minerva Chir*. 1990;45(17):1101-1106.

313. Dahan M, Boneu B, Renella J, Berjaud J, Bogaty J, Durand J. Prevention of deep venous thromboses in cancer thoracic surgery with a low-molecular-weight heparin: Fraxiparine. A comparative randomized trial. In: Bounameaux B, Samama M, and ten Cate JW, eds. Fraxiparine: Second International Symposium Recent Pharmacologic and Clinical Data. New York, NY: John Wiley & Sons Inc; 1990:27-31.

314. Encke A, Breddin K; The European Fraxiparin Study (EFS) Group. Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. *Br J Surg*. 1988;75(11):1058-1063.

315. Eurin B. Efficacy and tolerance of Fraxiparine in the prevention of deep vein thrombosis in general surgery performed with medullar conduction anesthesia [in French]. *Ann Fr Anesth Reanim*. 1994;13(3):311-317.

316. Fricker JP, Vergnes Y, Schach R, et al. Low dose heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery. *Eur J Clin Invest*. 1988;18(6):561-567.

317. Gallus A, Cade J, Ockelford P, et al. Orgaran (Org 10172) or heparin for preventing venous thrombosis after elective surgery for malignant disease? A double-blind, randomised, multicentre comparison. ANZ-Organon Investigators' Group. *Thromb Haemost*. 1993;70(4):562-567.

318. Garcea D, Martuzzi F, Santelmo N, et al. Post-surgical deep vein thrombosis prevention: evaluation of the risk/benefit ratio of fractionated and unfractionated heparin. *Curr Med Res Opin*. 1992;12(9):572-583.

319. Gazzaniga GM, Angelini G, Pastorino G, Santoro E, Lucchini M, Dal Prà ML; The Italian Study Group. Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. *Int Surg*. 1993;78(3):271-275.

320. Godwin J, Comp P, Davidson B, Rossi M. Comparison of the efficacy and safety of subcutaneous rd heparin vs subcutaneous unfractionated heparin for the prevention of deep-vein thrombosis in patients undergoing abdominal or pelvic-surgery for cancer. *Thromb Haemost*. 1993;69(6):647.

321. Haas S, Wolf H, Kakkar AK, Fareed J, Encke A. Prevention of fatal pulmonary embolism and mortality in surgical patients: a randomized double-blind comparison of LMWH with unfractionated heparin. *Thromb Haemost*. 2005;94(4):814-819.

322. Hartl P, Brücke P, Dienstl E, Vinazzer H. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. *Thromb Res*. 1990;57(4):577-584.

323. Hoffmann R, Largiader F. Perioperative prevention of thromboembolism with standard heparin and low molecular weight heparin, evaluation of postoperative hemorrhage. A double-blind, prospective, randomized and mono-center study [in German]. *Langenbecks Arch Chir*. 1992; 377(5):258-261.

324. Hoffmann R, Largiader F, Brutsch HP. Perioperative thromboembolic prophylaxis with low molecular weight heparin and postoperative bleeding complications [in German]. *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir*. 1990:1179-1184.

325. Kakkar VV, Boeckl O, Boneu B, et al. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. *World J Surg*. 1997;21(1):2-8, discussion 8-9.

326. Kakkar VV, Cohen AT, Edmonson RA, et al; The Thromboprophylaxis Collaborative Group. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. *Lancet*. 1993;341(8840):259-265.

327. Kakkar VVM, Murray WJ. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study. *Br J Surg*. 1985;72(10):786-791.

328. Kakkar VV, Stringer MD, Hedges AR, et al. Fixed combinations of low-molecular weight or unfractionated heparin plus dihydroergotamine in the prevention of postoperative deep vein thrombosis. *Am J Surg*. 1989;157(4):413-418.

329. Koller M, Schoch U, Buchmann P, Largiadèr F, von Felten A, Frick PG. Low molecular weight heparin (KABI 2165) as thromboprophylaxis in elective visceral surgery. A randomized, double-blind study versus unfractionated heparin. *Thromb Haemost*. 1986;56(3):243-246.

330. Koppenhagen K, Matthes M, Haring R, Troster E, Wolf H, Welzel D. Prophylaxis of thromboembolism in elective abdominal surgery. Comparison of efficacy and safety of low molecular weight heparin and unfractionated heparin [in German]. *Munch Med Wochenschr*. 1990;132(43):677-680.

331. Liezorovicz A, Picolet H, Peyrieux JC, Boissel JP; H.P.B.M. Research Group. Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin. *Br J Surg*. 1991;78(4):412-416.

332. Limmer J, Ellbrück D, Müller H, et al. Prospective randomized clinical study in general surgery comparing a new low molecular weight heparin with unfractionated heparin in the prevention of thrombosis. *Clin Investig*. 1994;72(11):913-919.

333. McLeod RS, Geerts WH, Sniderman KW, et al; Canadian Colorectal Surgery DVT Prophylaxis Trial investigators. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial. *Ann Surg*. 2001;233(3):438-444.

334. Moreno Gonzalez E, Fontcuberta J, de la Llama F. Prophylaxis of thromboembolic disease with RO-11 (ROVI), during abdominal surgery. EMRO1 (Grupo Fstudio Multicintrico RO-11). *Hepatogastroenterology*. 1996;43(9):744-747.

335. Nurmohamed MT, Verhaeghe R, Haas S, et al. A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *Am J Surg*. 1995;169(6):567-571.

336. Onarheim H, Lund T, Heimdal A, Arnesjø B. A low molecular weight heparin (KABI 2165) for prophylaxis of postoperative deep venous thrombosis. *Acta Chir Scand*. 1986;152:593-596.

337. Samama M, Bernard P, Bonnardot JP, Combe-Tamzali S, Lanson Y, Tissot E. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *Br J Surg*. 1988;75(2):128-131.

338. Sasahara AA, Koppenhagen K, Häring R, Welzel D, Wolf H. Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg*. 1986;73(9):697-700.

339. Schielke DJ, Staib I, Wolf H, Mankel T. Prophylaxis of thromboembolism in abdominal surgery. Effectiveness and tolerance of low molecular weight heparin in combination with dihydroergotamine. *Med Welt*. 1991;42(4):346-349.

340. Verardi S, Cortese F, Baroni B, Boffo V, Casciani CU. Role of low molecular weight heparin in the prevention of postoperative deep venous thrombosis. Our experience in 88 cases [in Italian]. *G Chir*. 1989;10(11):674-678.

341. Voigt J, Hamelmann H, Hedderich J, Seifert J, Buchhammer T, Köhler A. Effectiveness and side effects of low-molecular weight heparin-dihydroergotamine in preventing thromboembolism in abdominal surgery [in German]. *Zentralbl Chir*. 1986;111(21):1269-1305.

342. von Tempelhoff GF, Harenberg J, Niemann F, Hommel G, Kirkpatrick CJ, Heilmann L. Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin on cancer survival following breast and pelvic cancer surgery: A prospective randomized double-blind trial. *Int J Oncol*. 2000; 16(4):815-824.

343. Welzel D, Wolf H, Koppenhagen K. Antithrombotic defense during the postoperative period. Clinical documentation of low molecular weight heparin. *Arzneimittelforschung*. 1988;38(1):120-123.

344. Manso LC, Milheiro A, Castro e Sousa F. Prophylaxis of postoperative thromboembolism. Randomized prospective study [in Portuguese]. *Acta Med Port*. 1996;9(2-3):87-90.

345. D'Andrea B, Mancini T, Palmaccio A. Efficacy and tolerance of Fraxiparine in prevention of deep vein thrombosis in general surgery with spinal anesthesia (subarachnoidal and peridural) [in Italian]. *Rass Int Clin Ter*. 1995;75(12):554-562.

346. De A, Roy P, Garg VK, Pandey NK. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. *Blood Coagul Fibrinolysis*. 2010;21(1):57-61.

347. Koppenhagen K, Adolf J, Matthes M, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. *Thromb Haemost*. 1992;67(6):627-630.

348. Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest*. 2002;122(6):1933-1937.

349. Bounameaux H, Didier D, Polat O, Desmarais S, de Moerloose P, Huber O. Antithrombotic prophylaxis in patients undergoing laparoscopic cholecystectomy. *Thromb Res*. 1997;86(3):271-273.

350. Strömberg J, Sadr-Azodi O, Videhult P, Hammarqvist F, Sandblom G. Incidence and risk factors for symptomatic venous thromboembolism following cholecystectomy. *Langenbecks Arch Surg*. 2015;400(4):463-469.

351. Docherty PW, Goodman JD, Hill JG, et al. The effect of low-dose heparin on blood loss at abdominal hysterectomy. *Br J Obstet Gynaecol*. 1983;90(8): 759-763.

352. Poller L, McKernan A, Thomson JM, Elstein M, Hirsch PJ, Jones JB. Fixed minidose warfarin: a new approach to prophylaxis against venous thrombosis after major surgery. *Br Med J (Clin Res Ed)*. 1987;295(6609):1309-1312.

353. Allen NH, Jenkins JD, Smart CJ. Surgical haemorrhage in patients given subcutaneous heparin as prophylaxis against thromboembolism. *BMJ*. 1978; i(6123):1326.

354. Hedlund PO, Blombäck M. The effects of low-dose heparin treatment on patients undergoing transvesical prostatectomy. *Urol Res*. 1981;9(3):147-152.

355. Kutnowski M, Vandendris M, Steinberger R, Kraytman M. Prevention of postoperative deep-vein thrombosis by low-dose heparin in urological surgery. A double-blind, randomised study. *Urol Res*. 1977;5(3):123-125.

356. Vandendris M, Kutnowski M, Futeral B, Gianakopoulos X, Kraytman M, Gregoir W. Prevention of postoperative deep-vein thrombosis by low-dose heparin in open prostatectomy. *Urol Res*. 1980;8(4):219-221.

357. Fry DE, Pine M, Nedza S, Locke D, Reband A, Pine G. Hospital outcomes in inpatient laparoscopic cholecystectomy in Medicare patients. *Ann Surg*. 2017;265(1):178-184.

358. Collen JF, Jackson JL, Shorr AF, Moores LK. Prevention of venous thromboembolism in neurosurgery: a metaanalysis. *Chest*. 2008;134(2): 237-249.

359. Constantini S, Kanner A, Friedman A, et al. Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study. *J Neurosurg*. 2001;94(6):918-921.

360. Gruber UF, Rem J, Meisner C, Gratzl O. Prevention of thromboembolic complications with miniheparin-dihydroergotamine in patients undergoing lumbar disc operations. *Eur Arch Psychiatry Neurol Sci*. 1984;234(3):157-161.

361. Bauman JA, Church E, Halpern CH, et al. Subcutaneous heparin for prophylaxis of venous thromboembolism in deep brain stimulation surgery: evidence from a decision analysis. *Neurosurgery*. 2009;65(2):276-280, discussion 280.

362. Dermody M, Alessi-Chinetti J, Iafrati MD, Estes JM. The utility of screening for deep venous thrombosis in asymptomatic, non-ambulatory neurosurgical patients. *J Vasc Surg*. 2011;53(5):1309-1315.

363. Hacker RI, Ritter G, Nelson C, et al. Subcutaneous heparin does not increase postoperative complications in neurosurgical patients: An institutional experience. *J Crit Care*. 2012;27(3):250-254.

364. Glotzbecker MP, Bono CM, Wood KB, Harris MB. Thromboembolic disease in spinal surgery: a systematic review. *Spine*. 2009;34(3):291-303.

365. Macdonald RL, Amidei C, Baron J, et al. Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surg Neurol*. 2003;59(5): 363-372, discussion 372-374.

366. Prestar FJ. Prevention of thromboembolism complications with low molecular weight heparin in microneurosurgical lumbar intervertebral disk operations [in German]. *Neurochirurgia (Stuttg)*. 1992;35(1):1-4.

367. Voth D, Schwarz M, Hahn K, Dei-Anang K, al Butmeh S, Wolf H. Prevention of deep vein thrombosis in neurosurgical patients: a prospective double-blind comparison of two prophylactic regimen. *Neurosurg Rev*. 1992;15(4):289-294.

368. Lohmann U, Gläser E, Braun BE, Bötel U. Prevention of thromboembolism in spinal fractures with spinal cord injuries. Standard heparin versus low-molecular-weight heparin in acute paraplegia [in German]. *Zentralbl Chir*. 2001;126(5):385-390.

369. Tikkinen KAO, Craigie S, Agarwal A, et al. Procedure-specific risks of thrombosis and bleeding in urological non-cancer surgery: systematic review and meta-analysis. *Eur Urol*. 2018;73(2):236-241.

370. Eredics K, Wachabauer D, Röthlin F, Madersbacher S, Schauer I. Reoperation rates and mortality after transurethral and open prostatectomy in a long-term nationwide analysis: have we improved over a decade? *Urology*. 2018;118:152-157.

371. Gilfrich C, Leicht H, Fahlenbrach C, et al. Morbidity and mortality after surgery for lower urinary tract symptoms: a study of 95 577 cases from a nationwide German health insurance database. *Prostate Cancer Prostatic Dis*. 2016;19(4):406-411.

372. Reich O, Gratzke C, Bachmann A, et al; Urology Section of the Bavarian Working Group for Quality Assurance. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol*. 2008;180(1):246-249.

373. Foster HE, Barry MJ, Dahm P, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA Guideline. *J Urol*. 2018;200(3):612-619.

374. Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. II: Reduced dose of low molecular weight heparin. *Acta Obstet Gynecol Scand*. 1992;71(6):471-475.

375. Boncinelli S, Marsili M, Lorenzi P, et al. Haemostatic molecular markers in patients undergoing radical retropubic prostatectomy for prostate cancer and submitted to prophylaxis with unfractioned or low molecular weight heparin. *Minerva Anestesiol*. 2001;67(10):693-703.

376. Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. *Acta Obstet Gynecol Scand*. 1988;67(2):99-103.

377. Kaaja R, Lehtovirta P, Venesmaa P, et al. Comparison of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin, with or without dihydroergotamine, in abdominal hysterectomy. *Eur J Obstet Gynecol Reprod Biol*. 1992;47(2):141-145.

378. Theodorakis J, Fabricius PG, Marx FJ, Spannagel M, Schramm W. Low-molecular heparin in perioperative thromboembolism prophylaxis in urology - a prospective randomised study. *Blut*. 1990;60:143.

379. Briel RC, Doller P, Hermann CP. Prevention of thromboembolism in hysterectomies with low molecular weight heparin Fragmin [in German]. *Geburtshilfe Frauenheilkd*. 1988;48(3):160-164.

380. Tikkinen KAO, Craigie S, Agarwal A, et al. Procedure-specific risks of thrombosis and bleeding in urological cancer surgery: systematic review and meta-analysis. *Eur Urol*. 2018;73(2):242-251.

381. Kolluri R, Plessa AL, Sanders MC, Singh NK, Lucore C. A randomized study of the safety and efficacy of fondaparinux versus placebo in the prevention of venous thromboembolism after coronary artery bypass graft surgery. *Am Heart J*. 2016;171(1):1-6.

382. Spebar MJ, Collins GJ Jr, Rich NM, Kang IY, Clagett GP, Salander JM. Perioperative heparin prophylaxis of deep venous thrombosis in patients with peripheral vascular disease. *Am J Surg*. 1981;142(6):649-650.

383. Kulik A, Rassen JA, Myers J, et al. Comparative effectiveness of preventative therapy for venous thromboembolism after coronary artery bypass graft surgery. *Circ Cardiovasc Interv*. 2012;5(4):590-596.

384. Ho KM, Bham E, Pavey W. Incidence of venous thromboembolism and benefits and risks of thromboprophylaxis after cardiac surgery: a systematic review and meta-Analysis. *J Am Heart Assoc*. 2015;4(10):e002652.

385. Di Nisio M, Peinemann F, Porreca E, Rutjes AW. Primary prophylaxis for venous thromboembolism in patients undergoing cardiac or thoracic surgery. *Cochrane Database Syst Rev*. 2015; (6):CD009658.

386. Beghi C, Fragnito C, Antonelli A, et al. Prevention of deep venous thrombosis by a new low molecular weight heparin (Fluxum) in cardiac surgery. *Int Angiol*. 1993;12(4):383-386.

387. Farkas JC, Chapuis C, Combe S, et al. A randomised controlled trial of a low-molecular-weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing vascular surgery. *Eur J Vasc Surg*. 1993;7(5):554-560.

388. Speziale F, Verardi S, Taurino M, et al. Low molecular weight heparin prevention of post-operative deep vein thrombosis in vascular surgery. *Pharmatherapeutica*. 1988;5(4):261-268.

389. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev*. 2013; (3): CD008303.

390. Dennis JW, Menawat S, Von Thron J, et al. Efficacy of deep venous thrombosis prophylaxis in trauma patients and identification of high-risk groups. *J Trauma*. 1993;35(1):132-138, discussion 138-139.

391. Paffrath T, Wafaisade A, Lefering R, et al; Trauma Registry of DGU. Venous thromboembolism after severe trauma: incidence, risk factors and outcome. *Injury*. 2010;41(1):97-101.

392. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17(10):1-79.

393. Olson EJ, Bandle J, Calvo RY, et al. Heparin versus enoxaparin for prevention of venous thromboembolism after trauma: A randomized noninferiority trial. *J Trauma Acute Care Surg*. 2015;79(6):961-968, discussion 968-969.

394. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med*. 1996;335(10):701-707.

395. Cohn SM, Moller BA, Feinstein AJ, Burns GA, Ginzburg E, Hammers LW. Prospective trial of low-molecular-weight heparin versus unfractionated heparin in moderately injured patients. *Vasc Surg*. 1999;33(2):219-223.

396. Peedicayil A, Weaver A, Li X, Carey E, Cliby W, Mariani A. Incidence and timing of venous thromboembolism after surgery for gynecological cancer. *Gynecol Oncol*. 2011;121(1):64-69.

397. Ritch JM, Kim JH, Lewin SN, et al. Venous thromboembolism and use of prophylaxis among women undergoing laparoscopic hysterectomy. *Obstet Gynecol*. 2011;117(6):1367-1374.

398. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e227S-e277S.

399. Rogers FB, Shackford SR, Horst MA, et al. Determining venous thromboembolic risk assessment for patients with trauma: the Trauma Embolic Scoring System. *J Trauma Acute Care Surg*. 2012;73(2):511-515.

400. Scottish Intercollegiate Guidelines Network. Prevention and Management of Venous Thromboembolism: A National Clinical Guideline. SIGN publication No. 122. Available at: https://www.sign.ac.uk/assets/sign122.pdf. Accessed 10 December 2018.

401. National Institute for Health and Care Excellence. Venous Thromboembolism in Over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism. NICE guideline [NG89]. Available at: https://www.nice.org.uk/guidance/ng89. Accessed 10 December 2018.

402. Mont MA, Jacobs JJ, Boggio LN, et al; AAOS. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg*. 2011;19(12):768-776.

403. Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism--International Consensus Statement. *Int Angiol*. 2013; 32(2):111-260.

404. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an evidence-based guideline: a statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care*. 2016;24(1):47-60.

405. CLOTS Trials Collaboration, Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet*. 2009;373(9679):1958-1965.

406. Minocha J, Smith AM, Kapoor BS, et al; Expert Panel on Interventional Radiology. ACR Appropriateness Criteria® radiologic management of venous thromboembolism-inferior vena cava filters. *J Am Coll Radiol*. 2019;16(5S):S214-S226.

407. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e278S-e325S.

408. Liew NC, Alemany GV, Angchaisuksiri P, et al. Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism. *Int Angiol*. 2017;36(1):1-20.

409. Bang SM, Jang MJ, Kim KH, et al. Prevention of venous thromboembolism, 2nd edition: Korean Society of Thrombosis and Hemostasis Evidence-based Clinical Practice Guidelines. *J Korean Med Sci*. 2014;29(2):164-171.

410. Faraoni D, Comes RF, Geerts W, Wiles MD; ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: Neurosurgery. *Eur J Anaesthesiol*. 2018;35(2):90-95.

411. Violette PD, Cartwright R, Briel M, Tikkinen KA, Guyatt GH. Guideline of guidelines: thromboprophylaxis for urological surgery. *BJU Int*. 2016;118(3): 351-358.

412. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Frachgesellschaften e.V (AWMF). Prophylaxe der venösen Thromboembolie (VTE). Available at: https://www.awmf.org/uploads/tx_szleitlinien/003-001l_S3_VTE-Prophylaxe_2015-12.pdf. Accessed 10 December 2018.

413. Forrest JB, Clemens JQ, Finamore P, et al; American Urological Association. AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. *J Urol*. 2009;181(3):1170-1177.

414. Tikkinen KAO, Cartwright R, Gould MK, et al. EAU Guidelines on Thromboprophylaxis in Urological Surgery 2018. Available at: https://uroweb.org/wp-content/uploads/Thromboprophylaxis-2017-pocket.pdf. Accessed 10 December 2018.

415. Committee on Practice Bulletins--Gynecology, American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 84: Prevention of deep vein thrombosis and pulmonary embolism. *Obstet Gynecol*. 2007;110(2 Pt 1):429-440.

416. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. 2017;81:101-110.

417. Agency for Healthcare Research and Quality. Preventing Hospital-Associated Venous Thromboembolism: A Guide for Effective Quality Improvement, 2nd ed. AHRQ Publication No. 16-0001-EF. Available at: https://www.ahrq.gov/sites/default/files/publications/files/vteguide.pdf. Accessed 10 December 2018.